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Air Space Studies with Special Reference to Emphysematous Air Spaces

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Emphysematous air spaces long have been recognized as problems in diagnosis and treatment. Illustrating the difficulties has been the failure of roentgenography alone to establish suitable criteria for differentiation of air spaces from cavities due to disease *per se*. In the present paper there has been an attempt to elucidate the diagnoses through auscultation, pressure determinations and contrast media introduced by the transthoracic method.

These spaces have been classified as noted in Table 1. Blebs and bullae[1] in general are round or oval and in this study occurred mostly in the apical area. The alveolar spaces are much smaller. The basal emphysematous air spaces are much larger and more irregular in size and shape. In general they may be triangular, leaf or irregular in shape. The congenital cystic areas generally occur in upper lung fields and follow a lobular or lobar pattern. The solitary cysts probably are not true air spaces and not related to blebs and bullae and other emphysematous air spaces. This paper does not primarily deal with the classification of emphysema, nor does it propose a change in the classification. It only describes the x-ray findings in this study which fell into the divisions described above.

Statistical Data

Bronchiolar connections were demonstrated by x-ray film in approximately one-fourth of the cases, but no bronchial connections as in cavities (Table 2). Bronchiolar communications were three times more frequently demonstrated by pressures. Pressures in the pulmonary air spaces were atmospheric in 75 per cent, negative in 18 per cent and positive in 7 per cent (Table 3). Occasionally one pressure was experienced in one air space and upon advancing the needle to another space another pressure was encountered. Ordinarily atmospheric pressure would be expected, but it is easily conceivable that blockage of some of the bronchi may temporarily occur with absorption of air from the spaces to an extent that negative pressures would result. A positive pressure was encountered in only three cases, two of which had emphysema with

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TABLE 1—PULMONARY AIR SPACES

Classification	No.	per cent	Bronchiolar No.	Connections per cent
Blebs or Bullae	16	34.8	5	31
Alveolar Spaces	17	37.	3	18
Basal Emphysematous Spaces	6	13.	2	33
Congenital Cystic Area	3	6.5	0	0
Solitary Cyst	4	8.7	1	25
TOTAL	46	100	11	24

superimposed thoracoplasty and the other was a congenital cystic area with superimposed infection.

It must be kept in mind that these pressures were measured mostly in one air space, occasionally two and rarely three in the same lung. This would not be a fair representation of the pressures in all the air spaces of the lung. If enough were done it may approximate a fair representation of one case.

Blebs or bullae seem to be characteristically located in the apex near the supraclavicular fossae or near another cavity or large air space. The characteristic shape in this area is oval or round. This probably is due to the supraclavicular fossae limiting these to only a smaller branch of the bronchiole. These probably represent smaller clusters of alveoli which have ruptured and intercommunicated. Bronchiolar connections were noted in 31 per cent. Figure 1 represents one in the supraclavicular area.

Often-times in searching for air spaces none is found except expanded alveolar spaces as evidenced by atmospheric pressures. The contrast medium has been introduced in these, but does not form a distinct outline as in blebs or bullae; however, on x-ray film an indistinct density is outlined the size of which depends on the amount of contrast medium used. It may be that the alveolar spaces were filled and expanded by this

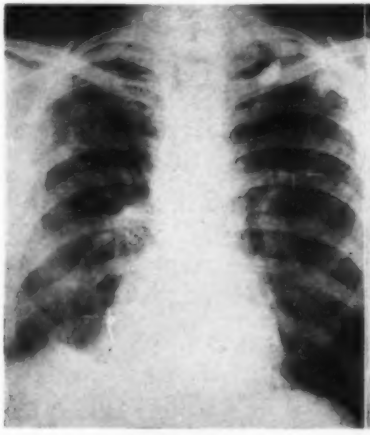

FIGURE 1

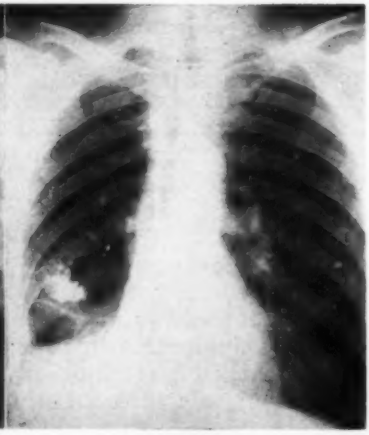

FIGURE 2

FIGURE 1: Oval air space more or less characteristic in supraclavicular area. Note another air space is medially and superiorly adjacent to the one demonstrated.
FIGURE 2: Large irregular basal air space with bronchiolar connection demonstrated.

contrast medium. No bronchial connection showed in 17 of these cases, but three bronchiolar connections were noted.

Although the above represents the results of emphysema and is part of the same process, the emphysematous air spaces seen in the basal and posterior portions of the lungs have a different appearance to blebs and bullae. They have a more or less triangular, leaf or irregular shape, are larger and more irregularly outlined. They probably represent a larger segment of the bronchiolar tree being involved. Figure 2 represents one of these segments as seen on x-ray with its bronchiolar connection. Figure 3 shows more irregularity and larger size as compared to blebs and bullae.

In the congenital cystic area there is more generalized distribution of the contrast medium. X-ray film shows a lobular or lobar distribution. No bronchiolar connections were seen in three cases. Figure 4 represents a chest x-ray film of this type of case. Note in the various air spaces demonstrated in this study no fluid level is formed by the contrast media as in cavities.

Discussion

The pressures of the various air spaces described have been found to be mostly atmospheric with a few negatives and less positives. Different pressures in the same patient in different spaces were noted. These group findings in 39 cases may be representative of the pressures that would be found in the average individual emphysematous patient, if it were possible to place the lumen of the needle in all the air spaces of the lung and measure the pressures. In these cases an atmospheric pressure was found in 75 per cent of the spaces, more or less. One probably could say as the percentage of open bronchi decreased, the severity of the condition would increase. However, it would be purely conjectural to state that if atmospheric pressures were present in only 50 per cent of the air spaces of the lungs, severe emphysema and shortness of breath would be present. Kuschner,[3] and others also have pointed out that actual anatomic

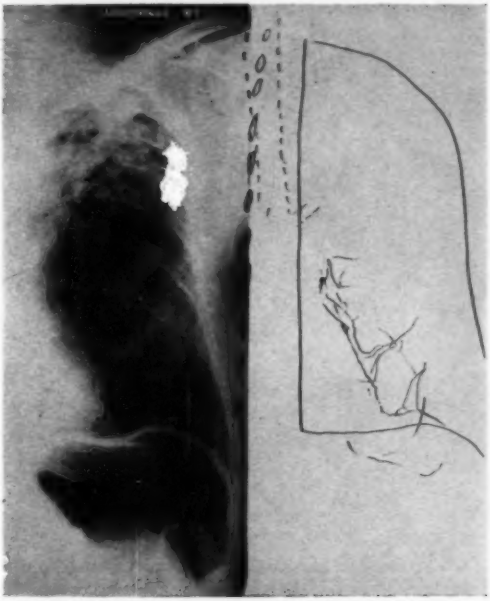

FIGURE 3: Large basal irregularly outlined air space. The super imposed drawing to right better illustrates the irregularity of the large emphysematous spaces.

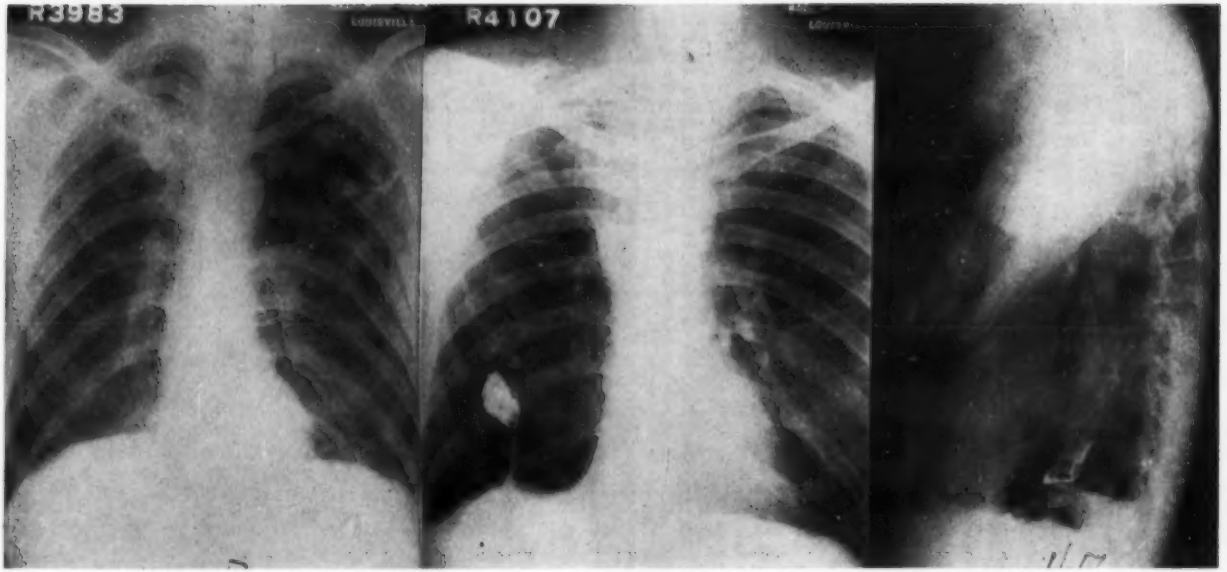

FIGURE 4 FIGURE 5 FIGURE 6

FIGURE 4: Congenital cystic area in left upper lobe outlined by Dionosil. FIGURE 5: Leaf shaped air space in base of right lung. FIGURE 6: Triangular shaped air space in base of left lung as seen on lateral film.

TABLE 2—PRESSURES* IN PULMONARY AIR SPACES

Classification		Atmospheric	Negative	Positive
Blebs and Bullae		10	3	1
Alveolar Spaces		10	2	
Basal Emphysematous spaces		4	1	1
Congenital Cystic Area		1	1	1
Solitary Cyst		3		
Bronchus		1		
TOTAL	47	29	7	3

*Pressures not registered in eight cases.

narrowing or intraluminal obstruction cannot be demonstrated, and yet there is ample physiological evidence of bronchial narrowing. In these cases there was indirect evidence of obstruction in approximately 25 per cent of the bronchi as shown by positive and negative pressures. There was direct evidence of non-obstruction in 24 per cent as shown by x-ray visualization of bronchioles.

It has been observed that the various types of air spaces secondary to the development of emphysema occur more frequently in the apex, posterior apex, posterior base and base. The findings in these studies may help to develop some theoretical considerations as to why these spaces localize where they do. It is not necessary to dwell here on the chronic bronchial infection or irritation, nor the change in blood supply that precedes emphysema. It should be stated that from a theoretical standpoint it is felt that cough plays a definite part in the production of air spaces. The following theoretical discussions are presented.

During the development of the cough process the contraction of the abdominal muscles depresses the anterior portion of the ribs and presses upward on the diaphragm. The initiation of pressure on the lungs is sudden in a posterior direction and upward from the diaphragm. While the pressure is increasing in the lungs in the above directions, the pressure in the apical, posterior and basal portions would be applied in the direction of the weakest portion of the alveolus. This would account for the destructive effect on the alveolus in these areas of the lungs in contra-distinction to that in the anterior area where the pressure is applied in the opposite direction. It is difficult to destroy an arch or break an egg when the pressure is applied in the direction of its greatest strength, but easy when applied in the opposite direction.

The next theory as to the development of these spaces is discussed as follows: It is observed on lateral x-ray film that these air spaces develop in the areas more peripheral from the main bronchus. Their development may be dependent on pressure gradients. These areas of the lungs are most distant from the main bronchi and the pressure gradient would be increased in them. Upon cough these would be the last and the least emptied and, therefore, the first and most injured by rupture.

The above theories may explain why emphysema localizes as it does; however, another condition plays a part in the production of these air spaces. It has been pointed out that there is an inequality of pressures in the air spaces as a result of obstruction. Whether one or the other or both of the above theories are true, the greatest effect or tear may occur in these spaces that have negative or positive pressures in the areas where there is the greatest strain. These are apical, posterior and basal in location. During the build-up of pressure in the lung for coughing, and until this pressure is released, there would be no difference in the intra-pulmonary pressures anywhere in the lungs. After the release of pressure, the air will escape faster and with more ease where there is no obstruction to the outlet. At this point an inequality of pressures will develop in the air spaces where there are negative or positive pressures. If a positive pressure is present in the blocked area, a rupture will be from within outward. If a negative pressure is present in the blocked area, a rupture would be from without inward. These inequalities of pressures in air spaces may cause distortion of the bronchial tree if there are many present. This would further obstruct or aggravate ventilation of this portion of the bronchial tree.

It is noted that air spaces in the apices, as outlined by contrast media, are generally round or oval in shape. In the base the emphysematous air spaces are larger and triangular, leaf or irregularly shaped. The location and physical properties present control the size and shape of these air spaces. During cough a small portion of the apex bulges at the supraclavicular fossa and limits the size and shape of the blebs and bullae. These are smaller segments of the bronchiolar tree and its alveolar clusters. Bullae also seem to develop near cavities or other air spaces but are not as round or oval as in the supraclavicular fossa. In the basal portion of the lungs there is no limiting factor like the supraclavicular fossa. The size and shape of air spaces will be governed by the size, shape and location of the smaller bronchiole and the area it supplies. This will explain its more or less irregular size and shape. Figures 5 and 6 are representative of these space areas.

From an x-ray film standpoint it is difficult to differentiate cavities from air spaces; however, these studies show many differences. Pulmonary cavities show open bronchial connections in 77 per cent of the cases. Air spaces show bronchiolar or small bronchial connections in 24 per cent of the cases in contra-distinction to those observed in pulmonary cavities. Pulmonary cavities have thick walls and air spaces no definite walls. Completely blocked cavities frequently show sinus tracts where none are seen in air spaces. No fluid level is formed by contrast media in air spaces as it does in cavities. The findings in air spaces are completely different to those in pulmonary cavities.

SUMMARY

1. Forty-seven cases of emphysematous air spaces have been studied by introducing contrast media, taking pressures and doing intrapulmonary auscultation.

2. These studies have demonstrated blebs, bullae, alveolar spaces, basal emphysematous spaces, congenital cystic areas and solitary cysts. Blebs and bullae appear to be more frequent in apical portion and the larger emphysematous air spaces in basal portion of the lungs.

RESUMEN

1. Cuarenta y siete casos de espacios enfisematosos se estudiaron introduciendo medios de contraste, midiendo las presiones y haciendo auscultación intrapulmonar.

2. Estos estudios han demostrado burbujas, bulas, espacios alveolares, espacios basales enfisematosos, áreas de quistes congénitos y quistes solitarios.

Las burbujas y las bulas aparecen mas frecuentemente en la región apical y los espacios enfisematosos mas grandes se ven en las bases.

RESUMÉ

1. 47 cas où existaient des zones aériques emphysémateuses ont été étudiés par introduction d'un milieu de contraste, avec mesure des pressions et auscultation pulmonaire.

2. Ces études ont mis en évidence des bulles, des zones alvéolaires, des zones d'emphysème, des zones kystiques congénitales et des kystes isolés. Les vèsicules et les bulles semblent être plus fréquentes dans la portion apicale et les zones aériques emphysémateuses plus développées dans la région basale des poumons.

ZUSAMMENFASSUNG

1. 47 Fälle mit emphysematösen lufthaltigen Lungenbezirken wurden untersucht mittels Einführung von Kontrastmedien, Druckmessung und intrapulmonaler Auskultation.

2. Diese Untersuchungen haben zum Nachweis kleinerer und größere Luftblasen, alveolärer Spalträume, basaler Emphysem-bildungen, congenitaler cystischer Bezirke und solitärer Cysten geführt. Die kleineren und größeren Blasen scheinen im Spitzenbereich und die größeren emphysematösen Veränderungen in den basalen Lungenabschnitten häufiger vorzukommen.

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2 Kuschner, Marvin: "Pathological Features of the Various Types of Emphysema," *A.M.A. Arch. Indust. Health*, 13:147, 1956.

ISOLATION OF THE RESPIRATORY SYNCYTIAL VIRUS FROM A PATIENT WITH PNEUMONIA

A virus with the characteristics of the respiratory syncytial virus was isolated from the throat of a six-month old infant with pneumonia. The illness was accompanied by an eightfold increase in complement-fixation antibody to the Long strain of the respiratory syncytial virus and a sixteenfold rise in the homologous neutralizating antibody, indicating that the pneumonia was accompanied by infection with this virus. The relationship between this infection and the patient's pneumonia is possibly etiologic.

Rowe, D. S., and Michaels, R. H.: "Isolation of the Respiratory Syncytial Virus from a Patient with Pneumonia," *Pediatrics*, 26:623, 1960.

Four and One-Half Years' Experience in the Treatment of Emphysema and Other Respiratory Insufficiencies by Tracheal Fenestration*,**

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Introduction

The purpose of this presentation is to report our experiences with tracheal fenestration in the treatment of pulmonary insufficiencies, covering a period of four and one half years. Since the first human application of this procedure on January 30, 1956, tracheal fenestration with effective tracheobronchial aspirations and self-aspirations proved to be of distinct help in the management of even end-stage cases of chronic respiratory diseases.[1-3,7,8]

Definition

Tracheal fenestration is a surgically created, air-tight, leakproof, skin-lined tracheocutaneous communication over the lower anterior cervical level.[9] The external opening of the skin tube is guarded by two valves which normally are in apposition. These valves may be manually opened and thus provide a shortcut entrance to the tracheobronchial tree for the purpose of aspirating retained secretion as well as instillation of medication. Tracheal fenestration does not interfere with phonation or the cough mechanism.

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TABLE 1—SUMMARY OF THE PREOPERATIVE STATUS OF THE PATIENTS

	Total	Male	Female	White	Colored	Cor Pulmonale	Cor Pulmonale in Failure
Pulmonary Insufficiency	36	28	8	29	7	27	9
Emphysema	32	27	5	28	4	26	9
Emphysema, "Dry"	11	11	—	10	1	9	3
Emphysema with Infection	21	16	5	18	3	17	6
Bullous Emphysema	3	2	1	3	—	2	2
Emphysema with Active Silico-TBC.	1	1	—	1	—	1	—
Cystic Fibrosis	2	1	1	1	1	—	—
Emphysema with Arrested TBC.	10	7	3	8	2	8	2
Active TBC.	3	2	1	1	2	2	—

Age Range: 2½ to 82 years Mean Age: 52 years

Clinical Material

To date we have treated 36 cases of pulmonary insufficiencies with this technic (Table 1). Of these, 28 were males and eight were females; 29 were white and seven were colored. Their ages ranged from two and one half to 82 years, with a mean age of 52 years. Twenty-seven of them had electrocardiographic evidence of cor pulmonale, and nine of these had clinical evidence of right-sided heart failure.

Thirty-two of the cases had emphysema, of which 27 were males and five were females. Twenty-eight were white and four were colored. Twenty-six of them had electrocardiographic evidence of cor pulmonale, and nine of these had clinical evidence of right-sided heart failure.

Eleven of the 32 emphysema cases had no history of cough or expectoration at any time. These are the so-called "dry" cases of emphysema. All of them were males. One was colored. Nine of them had electrocardiographic evidence of cor pulmonale, and three had clinical evidence of right-sided heart failure.

The remaining 21 of the 32 emphysema cases had cough and mucopurulent expectoration, and are grouped as emphysema with infection. Of them 16 were males and five were females. Eighteen were white and three were colored. Seventeen of them had electrocardiographic evidence of cor pulmonale, of whom six had clinical evidence of right-sided heart failure.

Twenty-nine of the 32 emphysema cases had diffuse hyperaeration of the lungs on x-ray inspection, and three of them had evidence of bullous emphysema. Of the latter, two were males and one was female.

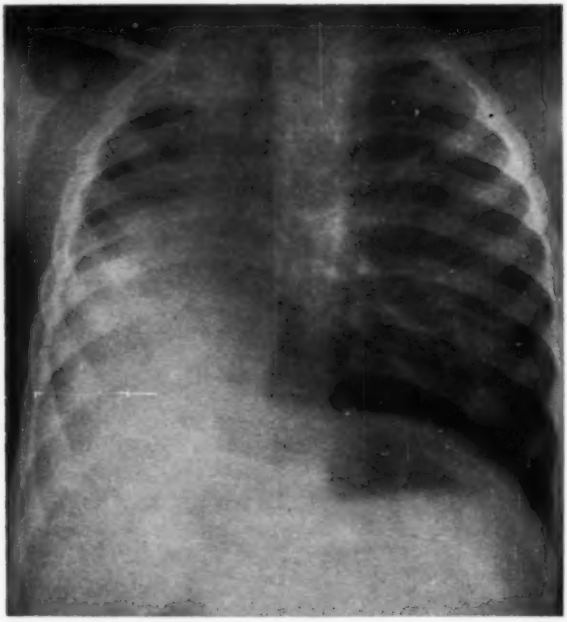

FIGURE 1: Chest x-ray film showing marked hyperaeration of the left lung and retraction of the mediastinum to the right.

All of them were white. Two of them had electrocardiographic evidence of cor pulmonale, and both had clinical evidence of right-sided heart failure.

One of the 21 cases of emphysema with infection had active silicotuberculosis. He was a white man with electrocardiographic evidence of cor pulmonale.

Ten of the 32 cases of emphysema had arrested pulmonary tuberculosis. Of these seven were males and three were females. Eight were white and two were colored. Eight of these 10 cases had electrocardiographic evidence of cor pulmonale, of whom two had clinical evidence of right-sided heart failure.

Two of the 36 cases of pulmonary insufficiencies had cystic fibrosis of the pancreas with excessive pulmonary suppuration. One of them was a white male and the other was a colored female.

Three of the 36 cases of pulmonary insufficiencies had active pulmonary tuberculosis. One of these is the case mentioned before with active silicotuberculosis. Of the three, two were males and one was female. One was white and two were colored. Two of these cases had electrocardiographic evidence of cor pulmonale.

Results

The clinical results are listed in Table 2. The terminology used in the evaluation of the cases is defined as follows:

Palliation was accomplished when the patients were made more comfortable than they were prior to the operation; exercise tolerance was increased; the respiratory and pulse rates were decreased; the color was improved.

Marked Palliation represented progressive improvement of pulmonary ventilation and exercise tolerance; oxygen was no longer required and the patients were fit for discharge from the hospital.

Rehabilitation was accomplished when the ventilation and exercise tolerance improved sufficiently to enable patients to undertake activities of daily living and attend to personal needs without oxygen or the assistance of others; these patients were able to walk a distance of several blocks without respiratory difficulties.

Marked Rehabilitation was accomplished when the patient's condition improved sufficiently to allow a return to some gainful occupation (if the patient so desired).

TABLE 2—SUMMARY OF THE POSTOPERATIVE STATUS OF THE PATIENTS

	Total	Operative Death	No Benefit	Palliation	Marked Palliation	Rehabilitation	Marked Rehabilitation
Pulmonary Insufficiency	36	1	1	14	9	6	5
Emphysema	32	1	1	10	9	6	5
Emphysema, "Dry"	11	—	—	4	3	1	3
Emphysema with Infection	21	1	1	6	6	5	2
Bullous Emphysema	3	—	1	2	—	—	—
Emphysema with Active Silico-TBC.	1	—	—	—	1	—	—
Cystic Fibrosis	2	—	—	2	—	—	—
Emphysema with Arrested TBC.	10	—	1	6	—	3	—
Active TBC.	3	—	—	3	—	—	—
Cor Pulmonale in Failure	9	—	—	6	3	—	—

One of the 36 cases of pulmonary insufficiencies died during the operation. This was a two and one half year old colored boy who underwent right pneumonectomy at the age of 15 months for atelectasis and bronchiectasis. Prior to the pneumonectomy and after bronchoscopy, tracheotomy was performed on this child. At the time of his tracheal fenestration, the site of the tracheotomy was healed. He had extensive suppurative disease and marked hyperaeration in his remaining lung (Figure 1) making him a cribridden respiratory cripple. He died of respiratory failure before the operation could be completed.

One of the patients had no appreciable benefit from tracheal fenestration with repeated tracheobronchial aspirations. She was a 58 year-old white woman with inactive, far-advanced pulmonary tuberculosis, resulting in advanced suppuration and bullous emphysema of the lungs. Her chest x-ray films (Figures 2a and 2b) show her lungs destroyed. Clinically she was gasping for air at rest in bed. Postmortem examination* revealed multiple residual cavitations in both lungs with marked bullous emphysema, mainly in the lower lobes. There was also pronounced fibrosis throughout the lungs. The "bronchi were filled with inspissated mucoid material." "Sections taken from the more consolidated areas show that the alveoli were filled with polymorphonuclear leukocytes, cellular debris and blood, matted with organized fibrin. Most of the terminal bronchioles in these areas are filled with cellular debris and polymorphonuclear leukocytes." She died seven days after the operation, of respiratory failure.

Fourteen of the 36 cases of pulmonary insufficiencies gained palliation which was marked in nine. Six of them were rehabilitated. Five were markedly rehabilitated.

Ten of the 32 cases of emphysema were palliated. Nine of them gained marked palliation. Six of them were rehabilitated. Five of them were markedly rehabilitated.

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TABLE 3—A LIST OF THE CAUSES OF DEATH

Bilateral Far Advanced Active Pulmonary Tuberculosis	3	(4.5, 8.5, and 1 Mo.)
Advanced Emphysema with Suppurative Disease of the Lungs	5	(3, 1.75, 23, 6 Mo. and 1 Wk.)
Respiratory Failure During the Operation	1	
Cystic Fibrosis	1	(1.75 Mo.)
Cerebrovascular Accident	1	(1.75 Mo.)
Carcinoma of the Lung	1	(1.5 Mo.)
Spontaneous Tension Pneumothorax	1	(8 Mo.)
Hemorrhage Due to Duodenal Ulcer	1	(2.5 Mo.)
Coronary Arterial Occlusion	1	(17 Days)
Pulmonary Embolism from Thrombophlebitis of Leg Vein	1	(2 Days)
Nephritis	2	(6 and 7.5 Mo.)
Staphylococcus Pneumonia	1	(6 Mo.)
Arteriosclerotic Heart Disease and Coronary Insufficiency	1	(19 Mo.)
Pneumonia and Right Heart Failure	1	(18 Mo.)
Suicide	1	(5 Mo.)
TOTAL	22	

Among the 11 so-called "dry" emphysema cases, four were palliated, three markedly so, one was rehabilitated, and three were markedly rehabilitated.

Among the 21 cases of emphysema with infection, six were palliated, six were markedly palliated, five were rehabilitated, and two were markedly rehabilitated. The one operative death and the one case without appreciable clinical benefit were in this group.

Two of the three bullous emphysema cases were palliated, and one had no benefit (the same case referred to in the paragraph preceding).

The one case of emphysema with active silicotuberculosis gained marked palliation.

Among the 10 cases of emphysema and arrested pulmonary tuberculosis, six were palliated and three were rehabilitated. The case without benefit was described above.

The two patients with cystic fibrosis of the pancreas and marked pulmonary suppuration were terminal cases, and only palliation was anticipated and gained.

One of the three active tuberculous cases gained marked palliation. The remaining two cases were palliated.

Among the nine cases of pulmonary insufficiencies with cor pulmonale in failure, six were palliated and three were markedly palliated.

Fourteen of the 36 cases are living. With respect to the others, the causes of death are listed in Table 3.

Three of the patients died of bilateral, far-advanced active pulmonary tuberculosis, 4.5 months, 8.5 months and 1 month respectively after operation.

Five of the patients died of respiratory failure due to far advanced emphysema with chronic suppurative bronchitis, 3 months, 1.75 months, 23 months, 6 months, and 1 week respectively after operation.

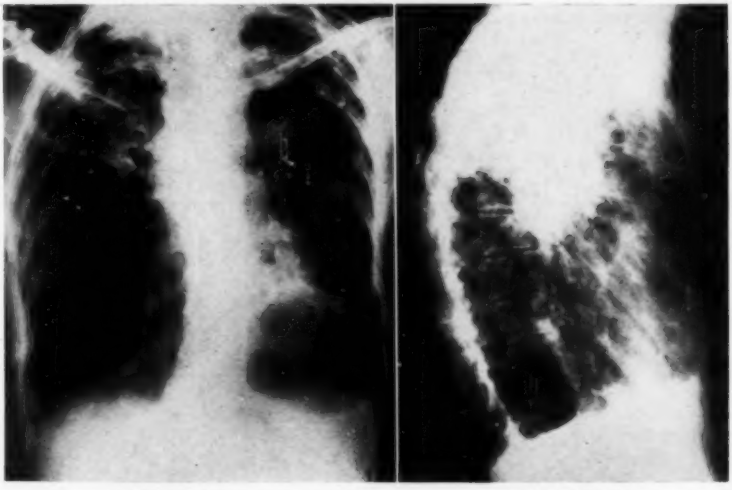

FIGURE 2A FIGURE 2B

FIGURES 2a and 2b: Posteroanterior and lateral chest x-ray films showing the lungs destroyed.

One child died of respiratory failure during operation. This is the case described in detail above.

One of the cystic fibrosis cases died of respiratory failure 1.75 months after the operation.

One died of a cerebrovascular accident 1.75 months after operation; one of cancer of the lung 1.5 months after operation; one of spontaneous tension pneumothorax eight months after operation; one of hemorrhage due to duodenal ulcer 2.5 months after operation; and one of massive coronary occlusion 17 days after the operation.

One child with cystic fibrosis died of pulmonary embolism from thrombophlebitis of a leg vein, two days after the operation.

Two died of glomerulonephritis, 6 months and 7.5 months respectively after the operation; one of staphylococcus pneumonia six months after operation; one of arteriosclerotic heart disease and coronary insufficiency, 19 months after the operation; one of pneumonia and right heart failure, 18 months after the operation; and one patient committed suicide because of failing eyesight, five months after the operation.

Case Reports

Case 1: (G.M.) A 52-year-old white man with history of progressive dyspnea for more than two years, had spontaneous pneumothoraces on the left side in March, May, and July, 1956, and chronic bronchitis on and off since childhood. Because of progressive dyspnea, he was hospitalized continuously for 18 months. He could not sleep through a night without awakening with air-hunger requiring oxygen. Walking only four or five steps would produce great air-hunger necessitating the use of oxygen. He had no cough and hardly any expectoration. On physical examination percussion revealed tympany over both lung fields. Breath sounds were depressed to absent. Posteroanterior and lateral chest x-ray films showed evidence of marked bilateral pulmonary fibrosis and diffuse hyperaeration (Figures 3a and 3b). Electrocardiogram showed evidence of cor pulmonale.

On October 28, 1957 he had tracheal fenestration. Because of the huge size of the sternocleidomastoideus muscles difficulties were encountered at operation, necessitating a second stage on November 4, 1957. Considerable amounts of thick, tenacious, stringy and glassy material was aspirated from the tracheobronchial tree right after intubation and during the operation. There were increasing amounts of aspirated material during the first postoperative week. With the second week this material began to decrease, and his daily self-aspirations of the tracheobronchial tree decreased accordingly. Within 24 hours after operation clear breath sounds could be heard over both lung fields and he was able to get out of bed. In a few days he was walking without dyspnea. By the time he was discharged from the hospital on April 3, 1958, he was able to walk up and down two flights of stairs without the least breathing difficulty. He was then aspirating himself only twice a day. Subsequently his exercise tolerance increased sufficiently to allow him to go to work as a communications clerk in September, 1958. From November 22, 1958 to December 11, 1958 he was hospitalized

TABLE 4—RESPIRATORY FUNCTION STUDIES OF CASE 2

	Observed			Predicted	Per Cent Predicted		
C.W.	Preop.	8 Weeks Postop.	10 Weeks Postop.		Preop.	8 Weeks Postop.	10 Weeks Postop.
Vital Cap.	1690	2397	2800	3829	44	63	73
Inspiratory Cap.	1210	1426	—	2872	42	49	—
Expiratory Reserve Vol.	480	972	—	957	50	101	—
Residual Vol.	—	3618	—	1421	—	255	—
Functional Residual Cap.	—	4616	—	2378	—	194	—
Total Lung Cap.	—	6015	—	5240	—	115	—
Maximum Breathing Cap.	15.2	28.5	—	101	15	27.8	—
Minute Ventilation	6	7.6	—	6.3	100	120	—
Tidal Vol.	400	485	—	350	114	139	—

TABLE 5—RESPIRATORY FUNCTION STUDIES OF CASE 2

C.W.	*Timed Vital Capacity*	
	Before Tracheal Fenestration	After Tracheal Fenestration (8 Weeks)
1 Sec.	39 per cent	48 per cent
2 Sec.	58 per cent	87 per cent
3 Sec.	70 per cent	99 per cent

with right lower lobe pneumonia. Continued effective tracheobronchial aspirations and self-aspirations aided his recovery and he has been working continuously for the past 18 months. He aspirates himself once or twice a day.

It is 32 months since his operation. Tracheal fenestration and repeated effective tracheobronchial self-aspirations led to complete rehabilitation of this respiratory cripple with advanced, diffuse, so-called "dry" emphysema. Apparently, peripheral bronchial and bronchiolar secretional occlusion rather than bronchial or bronchiolar spasm was the main source of his respiratory difficulties.

Case 2: (C.W.) A 59-year-old white man, former seaman and assistant building superintendent, hospitalized on November 9, 1959 because of progressive dyspnea, minimal cough and expectoration of 25 to 50 cc. clear, tenacious sputum daily. He had pneumonia six times in the past 35 years. He also had empyema on the left side requiring surgical drainage in 1947. In 1955 he was found to have bilateral chronic pulmonary tuberculosis. On chemotherapy tuberculosis was controlled and sputa have been negative on smear and culture since April, 1958. Inspection revealed a thin, dyspneic, cyanotic middle aged man using his accessory respiratory muscles. There was evidence of previous rib resection on left side. Physical examination revealed tympany and depressed to absent breath sounds over both lung fields.

Chest x-ray films (Figures 4a and 4b) revealed evidence of bilateral arrested pulmonary tuberculosis, diffuse hyperaeration of both lungs, depression of the diaphragms with fixation of the left diaphragm and obliteration of the left costophrenic sinus. An electrocardiogram showed evidence of cor pulmonale. Preoperative and postoperative respiratory studies and blood gas determinations are listed in Tables 4, 5 and 6.

On March 11, 1960 he underwent tracheal fenestration and simultaneous mediastinal tracheotomy. Recovery was uneventful, his wounds are healed. Breath sounds are clearly audible over both lung fields, exercise tolerance has increased remarkably, he can walk up and down four flights of stairs without dyspnea. He aspirates himself twice daily. He was discharged from the hospital on June 7, 1960 and referred for vocational rehabilitation.

This arrested case of chronic pulmonary tuberculosis has been completely rehabilitated by tracheal fenestration and effective tracheobronchial aspirations.

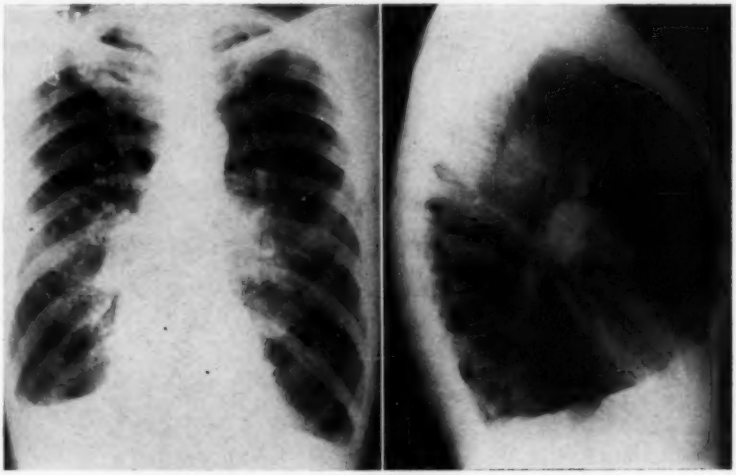

FIGURE 3A FIGURE 3B

FIGURES 3a and 3b: Posteroanterior and lateral chest x-ray films showing evidence of marked bilateral pulmonary fibrosis and diffuse hyperaeration of the lungs.

TABLE 6—BLOOD GAS ANALYSES OF CASE 2

C.W.	Before Tracheal Fenestration	After Tracheal Fenestration (8 Weeks)
Arterial O_2 Content	15.96	16.12
Arterial O_2 Saturation	92.	89.
Arterial CO_2 Content	53.1	48.81
Arterial O_2 Capacity	17.02	17.88

Case 3: (W.H.) A 59-year-old white man clerk with respiratory difficulties for over 20 years. He "caught a cold" three years ago; since then his breathing has worsened considerably. For six months past he has been having breathing difficulties at all times, even at rest, gasping for air on the least exertion. He has had no cough and no expectoration; started to smoke at the age of 18; now smoking 30 to 40 cigarettes per day; stopped smoking in January, 1960 without improvement in his breathing. He had marked inspiratory retraction of the lower intercostal spaces. Physical examination revealed tympany and depressed to absent breath sounds over both lung fields.

Chest x-ray films (Figures 5a and 5b) revealed marked diffuse hyperaeration of the lungs with diaphragms depressed. An electrocardiogram showed evidence of cor pulmonale. Preoperative and postoperative respiratory function studies and blood gas analyses are listed in Tables 7, 8 and 9.

On April 12, 1960 he underwent tracheal fenestration with simultaneous mediastinal tracheotomy. Right after intubation and before operation, tracheobronchial aspirations produced thick, tenacious, stringy, glassy material. During the first postoperative week, large quantities of secretion were aspirated from the tracheobronchial tree. Thereafter the daily secretions decreased gradually, and by the time of his hospital discharge on May 8, 1960, he required self-aspirations three or four times per day. His breath sounds became clearly audible and he could walk the hospital corridors without breathing difficulties. Two months postoperatively he could walk one city block without dyspnea. He sleeps through the night without awakening from air hunger, and can talk in continuity, which was not the case prior to operation. Operative wounds are healed and he aspirates himself three times daily.

This patient represents a typical so-called "dry" emphysema case who received marked palliation with tracheal fenestration and effective tracheobronchial aspirations.

Discussion

Tracheal fenestration *per se* does not do anything for the patient. If it is performed properly,[2,4,8,9] it does not reduce dead space, and it does not interfere with phonation or cough mechanism. It does provide a route for catheter insertions for effective

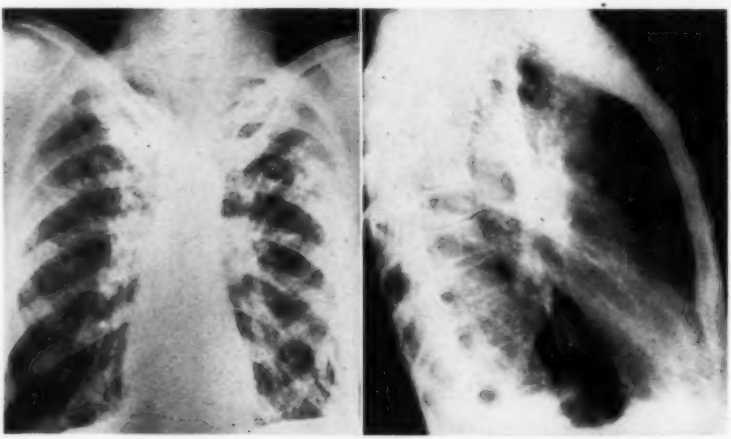

FIGURE 4A FIGURE 4B

FIGURES 4a and 4b: Posteroanterior and lateral chest x-ray films showing evidence of bilateral arrested pulmonary tuberculosis, diffuse hyperaeration of the lungs, depression of the diaphragms with fixation of the left diaphragm and obliteration of the left costophrenic sinus.

TABLE 7—RESPIRATORY FUNCTION STUDIES OF CASE 3

W.H.	Observed		Predicted	Per Cent Predicted	
	Preop.	4 Weeks Postop.		Preop.	4 Weeks Postop.
Vital Cap.	1938	2563	3630	53	71
Inspiratory Cap.	1378	1794	2722	51	66
Expiratory Reserve Vol.	560	768	907	62	85
Residual Vol.	6062	5935	1615	413	367
Functional Residual Cap.	7430	6495	2522	295	259
Total Lung Cap.	9225	7873	5245	175.8	150
Maximum Breath. Cap.	17.9	16.8	91	19.6	18
Minute Ventilation	6.1	11.8	6.95	88	169
Tidal Vol.	420	638	427	98	149

tracheobronchial aspirations and self-aspirations. All of our patients learned easily how to insert the catheters into the designated lungs or lobes, in so doing even reaching the segments within the designated lobes. The smaller catheters can reach beyond the subsegments, which explains why inspissated material within the peripheral airways can be removed by this technic. Tracheal fenestration as developed by us should not be performed unless the operator is willing also to apply our suctioning technic, using the catheters designed for this purpose (Figure 6).[4] Straight catheters will not reach designated lobes and segments within the designated lobes; therefore, their use might be only partially beneficial in cases of emphysema with infection, and would be completely without benefit in the so-called "dry" emphysema cases. It must be explained to patients that this is a "do-it-yourself" treatment, and unless they are willing to cooperate, they should not be selected for tracheal fenestration.

The often dramatic increase in the exercise tolerance of these patients with respiratory insufficiencies is accomplished by the effective elimination of retained secretion in the tracheobronchial tree. Since no additional form of therapy was applied in these cases, we must assume that retained and often inspissated secretion was the major cause of their respiratory disability.

During the postoperative period, breath sounds become more and more audible. This degree of audibility parallels the increase in exercise tolerance.

Pulmonary function studies and blood gas analyses are the desired objective means for evaluating the results. Unfortunately, a cardiopulmonary laboratory was not available to us until recently; therefore, only early results can be reported in Tables 4 to 9.

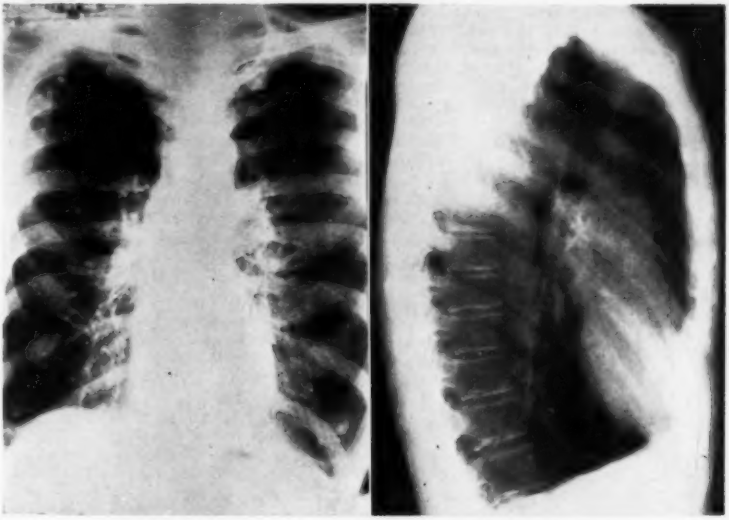

FIGURE 5A FIGURE 5B

FIGURES 5a and 5b: Posteroanterior and lateral chest x-ray films showing marked diffuse hyperaeration of the lungs with the diaphragms depressed.

TABLE 8—RESPIRATORY FUNCTION STUDIES OF CASE 3

W.H.	*Timed Vital Capacity*	
	Before Tracheal Fenestration	After Tracheal Fenestration (4 Weeks)
1 Sec.	25 per cent	29 per cent
2 Sec.	37 per cent	46 per cent
3 Sec.	48 per cent	62 per cent

In Case 2, the vital capacity increased considerably in 10 weeks. The rest of the respiratory studies also show improvement, particularly the maximum breathing capacity, which increased from a preoperative 15 per cent to a postoperative 27.8 per cent of the estimated normal in eight weeks (Table 4). Timed vital capacity also showed impressive changes (Table 5). The changes in blood gas analyses were not remarkable.

In Case 3, the vital capacity increased from a preoperative 53 per cent to a 4 weeks postoperative 71 per cent of estimated normal. There were notable changes also in the remaining respiratory studies listed in Table 7. The timed vital capacity showed marked improvement (Table 8). The changes in blood gas analyses are not remarkable (Table 9).

Pulmonary function studies and blood gas analyses should be done repeatedly and at regular intervals, and for a longer period of time in order to provide conclusive information. These preliminary data are presented only to give some idea of the direction of the anticipated long-term changes.

Tracheal fenestration with repeated tracheobronchial aspirations and self-aspirations proved quite effective in the treatment of diffuse emphysema with or without infection. Of the 29 cases in this group, 11 were rehabilitated. The other three of the total of 32 emphysema cases had bullous emphysema. The benefit in this group was limited (Table 2). In one of these three cases, tracheal fenestration was particularly helpful as a preparation for a subsequent left lower lobectomy.

Lack of cough and expectoration in a case of disabling diffuse emphysema is not a contraindication to this procedure, as we can see from the results in the 11 so-called "dry" cases of emphysema.

In active tuberculosis and cystic fibrosis, so far only palliation has been accomplished (Table 2). We had few opportunities to treat such cases. Particularly in cystic fibrosis, tracheal fenestration with effective tracheobronchial aspirations offers a new hope of long-term survival for these unfortunate children. Of course such cases should be submitted to this procedure before they become moribund.

Twenty-seven of the 36 cases of respiratory insufficiencies had electrocardiographic evidence of cor pulmonale. Nine of them were in rightsided heart failure. There was a distinct difference in the clinical course between those patients who were in rightsided heart failure and the rest of these cases. Their progress was slower and the maximum benefit was only marked palliation. They also require considerably more postoperative care than the others, since weeks elapse before they gain enough strength to do self-aspirations, in contrast to the rest of the cases who can start self-aspirations usually on the third postoperative day.

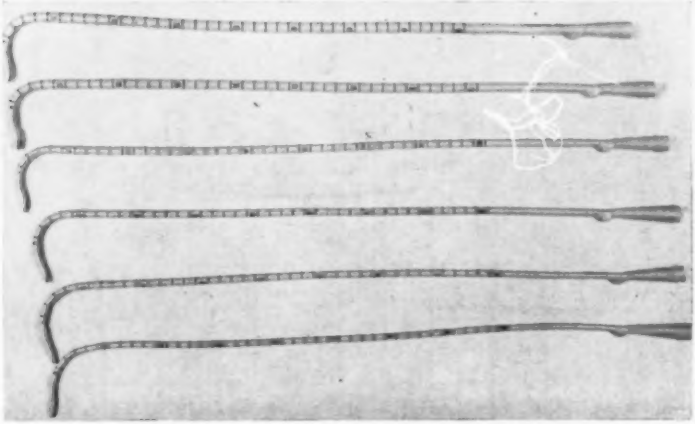

FIGURE 6: Photograph of a set (6) of Rockey-Thompson selective bronchial suction catheters.

TABLE 9—BLOOD GAS ANALYSES OF CASE 3

W.H.	Before Tracheal Fenestration	After Tracheal Fenestration (4 Weeks)
Arterial O_2 Content	15.15	13.47
Arterial O_2 Saturation	91.20	90.5
Arterial CO_2 Content	58.7	58.46
Arterial O_2 Capacity	16.27	14.65

On the basis of our encouraging experiences in the treatment of diffuse emphysema with tracheal fenestration and effective tracheobronchial aspirations, we feel justified in making a plea for this form of treatment in an earlier stage of this always progressive disease. We believe that those cases particularly who already present electrocardiographic evidence of cor pulmonale should be given the opportunity to be helped before they go into rightsided heart failure.

PRESENT INDICATIONS

1. Advanced cases of diffuse emphysema with or without cough and expectoration.
2. Excessive suppurative diseases of the lungs (such as bronchiectasis) when excisional surgery is contraindicated.
3. Fibrocystic disease of the pancreas with excessive pulmonary secretion.
4. Far advanced cases of pulmonary tuberculosis, for whom no other form of therapy can be offered.
5. Intractable bronchial asthma.

SUMMARY

Experience with 36 consecutive cases of respiratory cripples treated with tracheal fenestration and repeated tracheobronchial aspirations and self-aspirations is reported. Twenty-nine had diffuse emphysema, and three had bullous emphysema. Eleven of the 32 emphysema cases had so-called "dry" emphysema. Three had active pulmonary tuberculosis; one of them had active silicotuberculosis. Two had cystic fibrosis of the pancreas. Among these end stage cases of respiratory insufficiencies, the best response to this form of therapy was obtained in diffuse emphysema. Eleven of these cases were rehabilitated, and the rest of them were palliated or markedly palliated with two exceptions. One of these two gained no benefit and the other died before the operation could be completed. Pulmonary function determinations with early follow-up studies are reported. The present indications for tracheal fenestration are enumerated. Our observations during the past four and one half years confirm the initial impression that the major source of disability in advanced diffuse emphysema, including so-called "dry" emphysema, is secretional occlusion of the peripheral bronchi and bronchioles rather than bronchial and bronchiolar spasm.

ACKNOWLEDGEMENTS: We are indebted to Dr. Frank Borrelli, Director of Radiology, New York Medical College-Metropolitan Medical Center, New York, and staff, for the radiological work-up of the cases reported here.

We wish to express our appreciation to Dr. John Kovach, Director, Cardiopulmonary Laboratory, New York Medical College-Metropolitan Medical Center, New York, and staff, for the physiological studies reported in this paper.

We also wish to express our gratitude to Dr. Charles P. Bailey, Professor and Chairman, Department of Surgery, New York Medical College-Metropolitan Medical Center, New York, for his stimulating interest in and encouragement and support of this study.

RESUMEN

Se relata la experiencia llevada a cabo con 36 casos consecutivos de enfermos respiratorios incapacitados que se trataron con la fenestración traqueobronquial y las aspiraciones repetidas así como hechas por el mismo enfermo. Veintinueve tenían enfisema difuso y tres tenían enfisema buloso. Once de los 32 casos de enfisema tenían el llamado enfisema "seco." Tres tenían tuberculosis activa y uno de ellos silicituberculosis en actividad.

Entre estos casos terminales de insuficiencia respiratoria, la respuesta mejor se obtuvo entre los de enfisema difuso. Once de éstos casos pudieron rehabilitarse y el resto mejoraron notablemente con dos excepciones, uno de éstos que no obtuvo beneficio alguno y el otro que murío antes de que la operación se hubiera terminado.

Las determinaciones de la función pulmonar con seguimiento inmediato se relatan aquí. Se desecriben las indicaciones actuales para fenetración.

Nuestros observaciones durante los pasados cuatro años y medio confirman la impresión inicial de la causa mayor de la incapacidad en el enfisema difuso avanzado incluyen el llamado enfisema "seco" es la oclusión de los bronquios periféricos y de los bronquiolos por las secreciones mas que el espasmo bronquial y bronquiolar.

RESUMÉ

L'auteur rapporte l'expérience qu'il a acquise par l'étude de 36 cas de grande insuffisance respiratoire traitée par fenestration trachéale, aspirations trachéobronchiques répétées et auto-aspirations. 29 malades étaient atteints d'emphysème diffus, et trois avaient un emphysème bulleux. Onze cas sur les 32 emphysèmes avaient un emphysème dit "sec." Trois malades étaient atteints de tuberculose pulmonaire évolutive, l'un d'entre eux avait une silico-tuberculose évolutive. Deux étaient atteints de fibrose kystique du pancréas. Parmi ces cas déinsuffisance respiratoire à leur degré ultime, la meilleure réponse à cette forme de traitement fut obtenue dans l'emphysème diffus. Onze de ces cas furent réadaptés et le reste d'entre eux furent améliorés ou même considérablement améliorés, avec deux exceptions. L'un de ces deux cas ne tira aucun bénéfice du traitement et l'autre mourut avant que l'opération put être terminée. Des examens de la fonction pulmonaire avec bilan précoce sont rapportés. Les indications actuelles de la fenestration trachéale sont énumérées. Les observations de l'auteur pendant ces quatre dernières années confirment l'impression initiale que la source majeure de l'incapacité dans l'emphysème diffus grave, y compris l'emphysème dit "sec," est l'occlusion par les sécrétions des bronches périphériques et des bronchioles plutôt que le spasme bronchique et bronchiolaire.

ZUSAMMENFASSUNG

Es werden die Erfahrungen wiedergegeben an 36 aufeinanderfolgenden Fällen von schwerst geschädigter Atmung nach Behandlung mit Luftröhrenfensterung sowie wiederholten Tracheobronchialen-Aspirationen und Eigen-Aspirationen. 29 Patienten litten an einem diffusem Emphysem, und 3 ein bullöses Emphysem hatten. 11 von diesen 32 Emphysematikern hatten ein sogenanntes "trockenes" Emphysem. 3 hatten eine aktive Lungentuberkulose, einer von ihnen hatte eine aktive Silikotuberkulose. Zwei hatten eine cystische Pankreasfibrose. Unter diesen Endstadien respiratorischer Insuffizienzen erzielte man die besten Reaktionen auf diese Behandlungsform beim diffusen Emphysem. 11 von diesen Fällen wurden wieder hergestellt und arbeitsfähig. Die übrigen erfuhren eine mehr oder minder deutliche Linderung mit 2 Ausnahmen. Die eine von diesen besserte sich nicht, und der andere Patient starb, ehe die Operation zu Ende geführt werden konnte. Es wird über die Bestimmungen der Lungenfunktionen mit ersten Nachbeobachtungen berichtet. Die gegenwärtigen Indikationen für die Lufträhren fensterung werden aufgezählt. Unsere Beobachtungen während der vergangenen 4½ Jahre bestätigen den anfänglichen Eindruck, wonach die häufigere Ursache für die Arbeitsunfähigkeit beim fortgeschrittenen diffusen Emphysem einschliesslich dem sogenannten "trockenen" Emphysem gegeben ist in einem sekret-bedingten Verschluß der peripheren Bronchien und Bronchiolen und weniger in einem Spasmus der Bronchien und Bronchiolen.

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Preliminary Report: Epidemiology of Infections Due to the Atypical Acid-Fast Bacilli*,**,†

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Introduction

Max Pinner[1] in 1935 emphasized the need of a critical evaluation of the significance of atypical acid-fast micro-organisms isolated from human sources. He was among the first to suggest a possible cause-effect relationship between these "saprophytes" and human disease. Our knowledge concerning the "Atypical" (also designated the "Anonymous" or the "Unclassified") mycobacteria has increased considerably during recent years,[2-6] but the natural habitat and communicability of these organisms remain unknown.[7-11]

Since late 1955, in Florida we have been concerned with the mode(s) of transmission and source(s) of the atypical mycobacteria. It was evident from a pilot epidemiological investigation that a long-range exacting field study would be necessary. A research grant was approved by the National Institutes of Health and a formal study became fully established in April, 1959. Presently, our special study revolves about three intimately related primary objectives: the source, the methods of transmission and the person to person communicability of these organisms.

Most of the cases upon which this report is based have come to our attention because they were either known or suspected of having tuberculosis, or they were contacts of known tuberculosis cases. Our major case-identification procedure has been the isolation of atypical mycobacteria from routine specimens examined for *M. tuberculosis* by public health and tuberculosis hospital laboratories. Recently, the Veterans Administration Hospitals of Florida and several private and community hospitals have assisted by submitting any acid-fast organisms which appear to be "Atypicals." In addition, the increasing interest of Florida physicians, as well as our own epidemiological investigations, is resulting in the examination of specimens for acid-fast organisms from patients with a variety of pulmonary syndromes, patients with non-pulmonary disease and from people without manifest abnormality.

The atypical acid-fast organisms, as a group, are easily differentiated bacteriologically, from *M. tuberculosis*. They are subdivided into four groups designated with Roman numerals I (photochromogens), II (scotochromogens), III (non-photochromogens) and IV (rapid growers). The classification is based upon the work of Dr. Runyon[4] and depends upon the temperature requirements for growth of these organisms, their ability to produce various pigments when exposed to light, their rate

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of growth, their uniform avirulence for the guinea pig and their pathogenicity for certain other laboratory animals.

For this presentation, the terms "isolation," "infection" and "case" are used interchangeably and mean simply that atypical acid-fast bacilli have been cultured one or more times from the body fluids or tissues of a specific person. There may or may not be an associated pathologic process.

Distribution of Atypical Types

During the four years that the Florida laboratories have been studying this special group of bacteria, 585 cases have been identified (Table 1). Approximately 75 per cent of them are due to the Group III atypical mycobacteria, the non-photochromogens. Only 4.9 per cent are due to the Group I, photochromogens. Reports from elsewhere in the United States indicate that the non-photochromogens are found predominantly in the Southeast; other sections of the United States have reported more commonly on infections associated with the photochromogens. The more highly pigmented but slow growing scotochromogens were isolated from 12.6 per cent of our cases, while the rapid growers accounted for 9.3 per cent.

Age, Race and Sex

The age istribution is shown in Table 2. The atypical mycobacteria have been isolated only rarely from the young. They are found predominantly in the aged. Of our known cases, 51.8 per cent are above age 54; 88 per cent are above age 34. This distribution differs strikingly from that of the general population, as shown in the Table.

Table 3 presents the race and sex of these people. Approximately three-fourths are males. The white male is the group of largest number. The computed rates for 1959 (Table 4) suggest that the colored male has the higher attack rate. These observations must be interpreted with caution since the race and sex of the source of all specimens examined for acid-fast organisms during 1959 are not known. However, it is known that case finding procedures are more adequate for the white than for the colored race.

Variations in Incidence with Time

Figure 1 depicts the varying incidence of newly identified atypical infections since the beginning of our studies. There has been a gradual increase in incidence over the past five years. The obvious seasonal peak, which occurred in early 1959 and appears to be recurring in 1960, is

TABLE 1—IDENTIFIED ATYPICAL CASES BY TYPE—FLORIDA 1956-59

Atypical Type (Group)	Total Cases	
	No.	per cent
I	29	4.9
II	74	12.6
III	428	73.2
IV	54	9.3
TOTAL	585	100.0

particularly impressive. It is reasonable to suspect that a proportion of the gradual increase is due to increasing awareness of these organisms by the laboratories. The explanation of the seasonal peaks is not apparent. A variation in the number of examinations is not the basis: specimens submitted to public health and tuberculosis hospital laboratories for acid-fast studies do not vary significantly from approximately 3,000 per month, year round.

Geographic Considerations

There is evidence that infections due to the non-photochromogens are found predominantly in the Southeastern United States. The results of skin tests with the Battey Strain tuberculin (PPD-B) on Navy recruits and other groups by United States Public Health Service teams[12] provide strong support for this view.

In Florida, variations between counties of both rates of newly found infections and rates of positive reactors to Battey-tuberculin have been noted. Workers in Georgia find a similar county variation in their state.[13] Our data show that both of these indices are low in the countries of the lower east coast and at the southern tip. The rates (Figure 2) of newly reported cases for 1959 are low in the countries of the northwestern section of the state; however, limited studies in this area indicate a high rate of Battey-tuberculin reactors. The area with the highest rate of detected infections extends from the west-central counties of the peninsular portion of Florida northward through the central counties to the Georgia line. An indeterminate proportion of this distribution might be due to the alertness early in these studies of the Southwest Florida Tuberculosis Hospital at Tampa. This factor probably has no influence at this time because all the laboratories now appear equally effective in the isolation of these organisms.

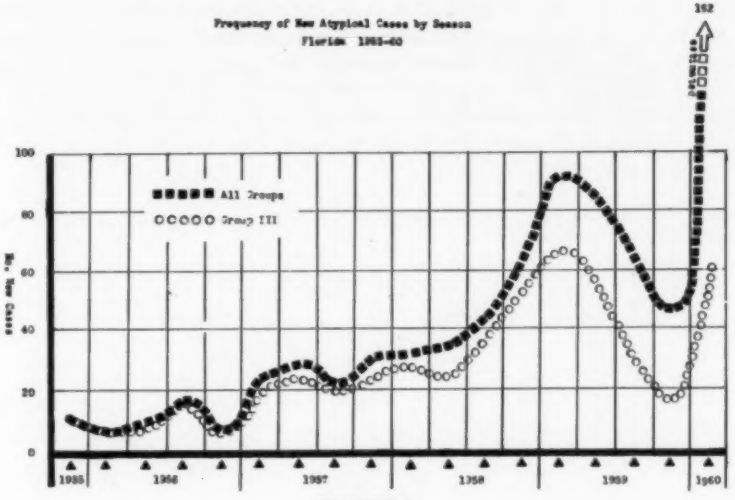

FIGURE 1

The 1959 rates by county have been computed for newly reported atypical infections and for newly reported tuberculosis cases. Table 5 lists the six counties with the lowest and the six counties with the highest rates of newly reported atypical cases. It is apparent to those familiar with the geography of Florida that the higher rates occurred in the more rural areas. The lowest rates occurred in the predominantly metropolitan counties. This observation is in sharp contrast to the picture of tuberculosis, a disease historically associated with crowding.

It is notable that a large proportion of our known cases were born on farms and have lived most of their lives in the rural southeast. Initial epidemiologic observations among the households of cases living in the northeast section of Florida show that 25 (96 per cent) of the 26 cases interviewed were born in one of the five southeastern states; 10 (38.6 per cent) of the 26 were born in their Florida county of residence. Sixteen (60 per cent) of these lived on farms. Eighty per cent of the households were rated in the moderate to very low socio-economic class. For the State generally, a large proportion of the cases follow occupations which are closely associated with the soil or which incur the inhalation of large quantities of dust.

Tuberculin Sensitivity

To gain further insight into the natural history of these infections, mass tuberculin surveys have been undertaken in selected sections of Florida. Table 6 reflects the results of Mantoux tests with typical (PPD-S) and atypical (PPD-B) tuberculins* among first and second grade public school children in three selected counties of Florida. The total of 1,677 children tested constitutes approximately 90 per cent of the entire first and second grade enrollment in these counties. Note that 1.1 per cent of this six to eight years age group was positive to PPD-S with induration above 8 millimeters. A significantly larger proportion of the children were positive to PPD-B: 6.6 per cent. There was no significant racial difference found among this group of PPD-S reactors; however, 16.4 per cent of the colored children and 3.5 per cent of the white children were positive to PPD-B. It was noted above that the colored race was found to have the higher attack rate of overt disease associated with these infections.

*Special tuberculins furnished by Dr. Lydia B. Edwards of the United States Public Health Service.

TABLE 2—IDENTIFIED ATYPICAL CASES BY AGE—FLORIDA 1956-59

Age	Cases		Estimated Population*	
	No.	per cent	No.	per cent
1-14	12	2.1	1,339,836	29.0
15-34	46	7.8	1,256,315	27.3
35-54	212	36.2	1,194,066	25.9
55-Up	303	51.8	820,383	17.8
Unknown	12	2.1		
Totals	585	100.0	4,610,600	100.0

*July 1, 1959 Estimate

A sputum specimen was obtained by aerosol bronchial lavage from most of these children reacting positively to either or both antigens. To date cultural studies have been completed on 75 of them: one (1.3 per cent) yielded an acid-fast organism—a non-photochromogen. Chest x-ray on this child was normal. There was no history of pulmonary or any other disorder.

In all, 69 of these children reacting positively to either or both antigens have been x-rayed. Sixty-seven (97.1 per cent) were without any roentgenographic sign of abnormality. Two (2.9 per cent) demonstrated diagnostic evidence of active primary tuberculosis. These were non-related, non-associated colored females who attended different schools. One of them was positive to both antigens with 26 mm. induration to PPD-S and 16 mm. to PPD-B. Of more interest was the other child who reacted only to PPD-B with 17 mm. induration. The bronchial lavage specimen from each of these was negative on culture.

Tests on Contacts

The household associates of 55 school children who were positive to PPD-B alone, 14 school children who were positive to PPD-S alone and

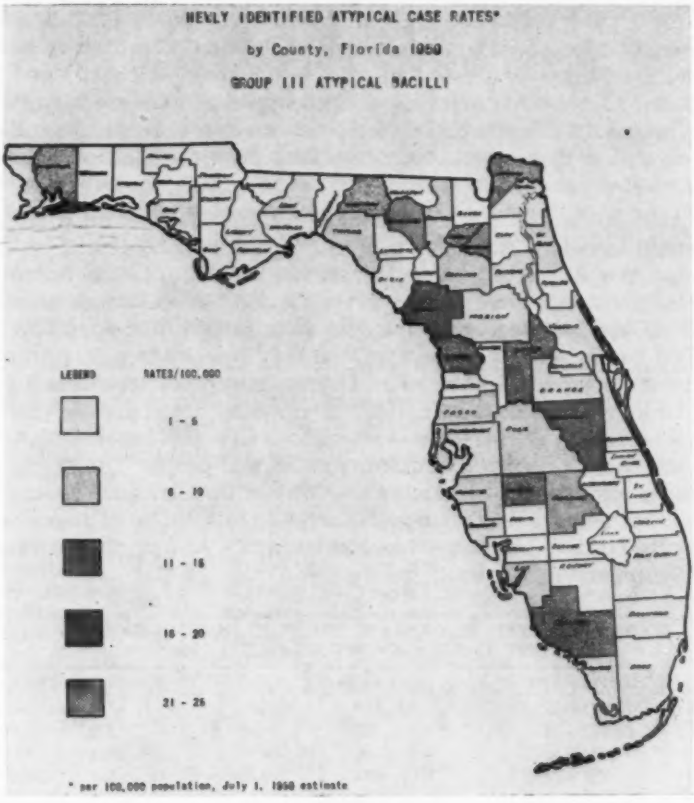

FIGURE 2

TABLE 3—IDENTIFIED ATYPICAL CASES BY RACE AND SEX—FLORIDA 1956-59

	White		Non-White		Totals	
	No.	per cent	No.	per cent	No.	per cent
Male	312	53.3	100	17.0	412	70.3
Female	116	19.9	57	9.7	173	29.6
Totals	428	73.2	157	26.7	585	100.0

the contacts of 80 patients known to be infected with non-photochromogenic atypical acid-fast bacilli were examined with tuberculin tests, chest x-ray films and sputum cultures. The results of these studies are summarized in Table 7.

One hundred and ninty-one household contacts of the 55 school children positive to PPD-B were tested with both PPD-B and PPD-S. Fifty-seven (29.8 per cent) were positive to PPD-B with induration above 8 millimeters; only nine (4.7 per cent) were positive to PPD-S. Forty-six household associates of the 14 school children positive to PPD-S were tested with these two tuberculins: eight (17.3 per cent) were positive to PPD-S and six (13.0 per cent) were positive to PPD-B. It is recognized that these studies need to be extended; nevertheless, the preliminary figures indicate a definite family clustering of persons exposed to non-photochromogenic atypical organisms or to antigentically similar agents.

Ninety-two household associates of the 69 school children reacting positively to either of these two tuberculins received chest x-ray films. Only one (1.1 per cent) demonstrated roentgenographic signs suggesting tuberculosis. This individual and one of the two children diagnosed as primary tuberculosis were both members of the same household and contacts of a known tuberculosis case.

Sputum specimens for bacteriologic culture were obtained from 119 household associates of the 69 tuberculin positive school children. These included 43 specimens obtained by aerosol bronchial lavage on children between the ages of five and 13 years. Of the 119 specimens, three (2.5 per cent) yielded acid-fast organisms—non-photochromogenic atypical acid-fast bacilli. Two of these were isolated from children. The third was isolated from an adult white man. One of the two bacteriologically positive children was a sibling of the only student (noted above) yielding a positive culture. These three bacteriologically positive children lived close together in a small community of colored people. The single adult yielding a positive culture reacted to PPD-B with 10 mm. induration, and was the father of a PPD-B positive school child. None of these bacteriologically positive persons demonstrated x-ray film or clinical evidence of any pulmonary disorder.

TABLE 4—ATYPICAL CASES IDENTIFIED DURING ONE YEAR BY RACE AND SEX—FLORIDA 1959

Race and Sex	Total Cases	Cases/100,000*
WM	139	7.6
WF	56	3.0
CM	46	10.3
CF	27	5.7

*Estimated Population

To date, tuberculin tests, chest x-ray films and sputum cultures have been made on household associates of 80 patients with known pulmonary pathology and associated infection with non-photochromogens (Table 7). Fifty-two of these contacts were skin tested with PPD-B: 10 (19.2 per cent) were positive with induration above 8 millimeters. Of 182 contacts tested with PPD-S, seven (3.8 per cent) were positive. Two hundred and thirty-four household associates received chest roentgenograms: 10 (4.2 per cent) had evidence suggestive of a past tuberculous process.

To date, sputum has been obtained for bacteriologic examination from household contacts of only three patients with non-photochromogenic atypical bacilli. Thirteen specimens, in all, were examined: two (15.4 per cent) were positive. It is notable that both of these, each identified as non-photochromogens, came from the same household. This particular family group is of special interest. The index case, an elderly colored man, came to our attention because a survey photofluorogram was read as suspicious of active tuberculosis. Follow-up studies yielded a non-photochromogenic atypical Mycobacterium. On the basis of this positive culture he was admitted to a state tuberculosis hospital. Multiple sputum examinations and gastric lavage specimens failed to yield an additional isolation. After six months hospitalization and exhaustive accessory studies, including negative tuberculin tests with PPD-S and PPD-B, he was discharged with the final diagnosis "no evidence of tuberculosis." Skin tests with PPD-B and PPD-S on 11 of his 13 household contacts yielded only one positive—his wife. She developed 13 mm. induration to PPD-B and was completely negative to PPD-S. Aerosol bronohial lavage specimens from five household members were positive in only the two mentioned above: the wife and a 26 year old daughter. X-ray films on the five adult members of the household failed to demonstrate any abnormality. No member of the family complained of pulmonary symptoms.

To summarize these observations on household groups in which there is positive evidence (by culture) or suggestive evidence (by PPD-B positivity) of a present or past infection with atypical acid-fast bacilli, we

TABLE 5—NEWLY IDENTIFIED ATYPICAL CASES AND NEWLY IDENTIFIED TUBERCULOSIS CASES—COUNTIES WITH LOWEST AND HIGHEST RATES FOR ATYPICAL CASES—FLORIDA 1959

County of Residence	Population 1959 Estimated	Cases/100,000 Population*		
		Atypical		
		All Groups	Group III	Tuberculosis
Duval	437,100	8.9	3.7	42.3
Hillsborough	373,900	6.7	5.3	41.7
Escambia	167,600	4.2	4.2	37.6
Palm Beach	223,500	4.0	2.2	42.5
Pinellas	323,100	3.1	1.5	32.8
Dade	855,800	2.3	1.2	37.3
Hardee	13,500	51.9	14.8	29.6
Osceola	18,300	32.8	16.4	32.8
Bradford	12,900	31.0	23.3	38.8
Levy	10,100	29.7	19.8	19.8
Lake	52,800	26.5	15.2	43.6
Nassau	15,500	25.8	12.9	25.8

*Estimated Population

would note that more than 500 presumably healthy contacts have been examined. Approximately 25 per cent of those tested were positive to PPD-B. Of the 132 examined bacteriologically, five (3.8 per cent) yielded non-photochromogenic atypical bacilli. Only 11 (3.4 per cent) of 326 examined by x-ray film had evidence of a present or past pulmonary disease.

Pathology Associations

Adequate clinical records have been obtained, to date, on 386 (90 per cent) of the 428 persons in Florida from whom non-photochromogens have been isolated. In only 146 (38 per cent) of the 386 cases is there reasonably secure evidence of a primary cause-effect relationship between the atypical organism and demonstrable pathology. Four of these had evidence of acid-fast disease of the kidney and 142 had x-ray evidence of pulmonary pathology. All yielded only non-photochromogens upon repeated examinations and no other cause for the disease state has been identified. Sixteen (4 per cent) of the 386 cases are without any apparent abnormality, either radiologically or clinically. The remaining 224 (58 per cent) either have bacteriological and/or clinical confirmation of other primary or associated causes to explain the manifest disease (e.g., *M. tuberculosis* or other specific disease), or lack sufficient evidence to securely incriminate the atypical organism (e.g., only single isolations from multiple examinations).

Evidence justifying an assumption of a primary etiological relationship between the non-photochromogen isolated and pulmonary disease was obtained in less than one-half of the cases. The frequency with which these organisms were found in persons with other demonstrable causes of pulmonary disease was impressive. In many patients other pulmonary disease or altered pulmonary function appeared to precede infection with these atypical mycobacteria. Cases coming to our attention were almost exclusively those being examined for Mycobacterium because of chronic pulmonary disease in the individual or in the family. Even so, we have suggestive evidence that these organisms have an etiological role in other diseases; for example, in chronic infections of the kidney and in some cases of acute self-limited pneumonitis. Furthermore, even

TABLE 6—RESULTS OF SKIN TESTS WITH PPD-S AND PPD-B IN FIRST AND SECOND GRADES OF SELECTED PUBLIC SCHOOLS—FLORIDA 1959-60

County	Race	No. Tested	Positive Reactors* PPD-S† No.	PPD-S† per cent	PPD-B‡ No.	PPD-B‡ per cent
1	White	930	12	1.3	38	4.0
	Colored	215	4	1.9	35	16.3
2	White	185	1	0.5	3	1.6
	Colored	143	2	1.4	20	13.9
3	White	160	0		4	2.5
	Colored	44	1	2.2	11	25.0
Totals	White	1,275	13	1.0	45	3.5
	Colored	402	7	1.7	66	16.4
Grand Totals		1,677	20	1.1	111	6.6

*9 mm. or more induration

†PPD-S—Standard Tuberculin (Typical), 5 T. U.

‡PPD-B—Battey Strain Tuberculin (Atypical), 5 T. U.

TABLE 7—RESULTS OF CONTACT EXAMINATIONS IN HOUSEHOLD ASSOCIATES OF PERSONS WITH SUGGESTED OR MANIFEST ATYPICAL ACID-FAST INFECTIONS—FLORIDA 1959-60

Index Cases		Tuberculin Tests						X-Rays			Cultures		
		PPD-B			PPD-S								
			Positive*			Positive*			Positive†			Positive‡	
Type	No.	No. Exam.	No.	per cent	No. Exam.	No.	per cent	No. Exam.	No.	per cent	No. Exam.	No.	per cent
School Child with Pos. PPD-B	55	191	57	29.8	191	9	4.7	76	1	1.3	93	3	3.2
School Child with Pos. PPD-S	14	46	6	13.0	46	8	17.3	16	0	0	26	0	0
Known Case with Pulmonary Patho. & Group III AAFB	80	52	10	19.2	182	7	3.8	234	10	4.2	13	2	15.4
TOTALS	149	289	73	25.2	419	24	5.9	326	11	3.4	132	5	3.8

*9 mm. or more induration

†Evidence of Tuberculosis pathology

‡Mycobacteria (All isolations were Group III Atypical Mycobacteria)

though sputum specimens are rarely submitted from normal people, still 16 (3.7 per cent) of those yielding this organism had neither symptoms nor signs of disease. In our epidemiological studies, as reported above, non-photochromogenic atypical mycobacteria were isolated from six additional "normals." To better define the true distribution of these organisms in man will require extensive and laborious bacteriological examinations of representative normals and of persons with a variety of disorders, as well as tuberculosis suspects. Obviously the basic pathogenesis of these organisms needs clarification.

Comment

It appears that the non-photochromogenic atypical organisms are widely distributed. If it can be assumed that PPD-B sensitivity is indicative of past exposure to these organisms, results of tuberculin tests indicate that these are not uncommon infections and that a fairly large percentage of the population comes in contact with them early in life. Our limited epidemiological data suggest a familial clustering of these infections; but there is no evidence that they are commonly transmitted from human to human. Regarding their source, there is reason to suspect an extra-human reservoir, perhaps the soil. The atypical mycobacteria have been found associated with acute processes frequently enough to raise the question whether they play a causative role in pulmonary disease of short duration. The histories of many cases support the view that the non-photochromogenic atypical acid-fast bacilli are "opportunists" and become capable of producing serious respiratory disease only after the normal pulmonary resistance has been lowered due to other causes. Place of birth, place of residence, occupation, race, age and associated diseases all appear related to frequency of infection by non-photochromogens but these relationships are ill-defined and poorly understood. The seasonal variation in incidence of newly found cases, as observed in these studies, is striking but unexplained.

SUMMARY

1. The atypical mycobacteria are distinct bacteriologic entities differing from *M. tuberculosis* both in cultural and biochemical characteristics and in animal pathogenicity. They need to be more adequately defined bacteriologically.

2. The atypical mycobacteria need to be considered as actual or potential human pathogens with variations in pathogenicity by groups. They are less capable than *M. tuberculosis* of producing progressive pulmonary disease.

3. Of all our known cases, elderly white men constitute the group of largest number. Preliminary data suggest that the colored race, and especially the colored male, has the higher attack rate.

4. Men who were born and have lived most of their lives in the rural southeast are most commonly involved with the non-photochromogens.

5. People found to harbor these organisms belong chiefly to the low socio-economic stratum.

6. There is in our series a distinct seasonal variation in the occurrence and/or recognition of newly identified cases.

7. The available data suggest a clustering by families of those exhibiting evidence of exposure to these bacteria, but conclusive evidence of transmission from man to man has not been obtained.

8. The habitat of these organisms remains uncertain; they could be derived from an extra-human source—possibly the soil.

9. Production of overt disease by these bacteria may be related to previous pulmonary abnormality and lowered pulmonary resistance.

10. All aspects of these infections must have additional study.

RESUMEN

1. Las micobacterias antípicas son entidades bacteriologicas que difieren del micobacterium tuberculosis tanto en los cultivos como en las características bioquímicas y su patogenicidad en los animales.

2. Las micobacterias atípicas necesitan considerarse como verdaderos patógenos humanos con variaciones en su patogenicidad por grupos.
Son menos capaces de producir enfermedad pulmonar progresiva que el M. tuberculosis.

3. De todos los casos conocidos el grupo mayor se encuentra entre los ancianos de raza blanca. Los datos preliminares sugieren que los negros y entre ellos en particular el hombre, tienen la mayor proporción de incidencia.

4. Los hombres que han nacido y han vividos el mayor tiempo en el sudeste rural, son los mas frecuentemente afectados por los no fotocromógenos.

5. Las personas en quienes se encuentran mas estos gérmenes son las de baja posición socio-económica.

6. En nuestras series hay una clara variación estacional en la ocurrencia y en el reconocimiento de los nuevos casos identificados.

7. Los datos con que se cuenta sugieren un agrupamiento por familias de los que muestran evidencias de exposición a esas bacterias, pero no se ha obtenido prueba concluyente de la transmisión de hombre a hombre.

8. El habitat de estos organismos permanece incierto; pueden ser derivados de una fuente extrahumana, posiblemente el suelo.

9. La producción de enfermedad franca por esas bacterias puede estar en relación con alguna anormalidad previa pulmonar y por el descenso de la resistencia.

10. Todos los aspectos de estas infecciones requieren estudio ulterior.

RESUMÉ

1. Les mycobactéries atypiques sont des entités bactériologiques distinctes du *M. tuberculosis* à la fois par leur caractère de culture, par leur nature boichimique, et par leur action pathogène chez l'animal. Elles demandent à être déterminées bactériologiquement avec une plus grande précision.

2. Les mycobactéries atypiques doivent être considérées comme des germes actuellement pathogènes pour l'homme ou susceptibles de le devenir avec des variations du pouvoir pathogène selon les groupes. Elles sont moins aptes à produire une maladie pulmonaire évolutive que le *M. tuberculosis*.

3. Sur tous les cas connus par l'auteur, les hommes âgés de race blanche constituent le groupe le plus important. Des constatations préliminaires font penser que la race de couleur, et particulièrement les individus de sexe masculin, a le taux d'atteinte le plus élevé.

4. Les hommes qui sont nés et ont vécu la plupart de leur vie dans le sud-est rural sont le plus communément atteints des germes non-photochromogènes.

5. Les porteurs de ces germes appartiennent principalement aux couches sociales les plus défavorisées.

6. Dans notre série il y a une variation saisonnière nette dans l'apparition et/ou la reconnaissance de cas nouvellement identifiés.

7. Les constatations valables font penser que ceux qui ont été exposés à ces bactéries appartiennent à certains groupes familiaux mai son n'a pu obtenir une preuve concluante de la transmission d'homme à homme.

8. L'habitat de ces germes reste indéterminé; ils pourraient provenir d'une source extra-humaine, peut-être le sol.

9. La production d'une affection manifeste par ces germes peut avoir pour origine une anomalie pulmonaire antérieure et un affaiblissement de la résistance pulmonaire.

10. Tous les aspects de ces infections justifient des études complémentaires.

ZUSAMMENFASSUNG

1. Die atypischen Mykobakterien sind deutliche bakteriologische Wesenheiten und unterscheiden sich vom *M. tuberculosis* sowohl durch kulturelle als auch biochemische Merkmale und hinsichtlich der Tierpathogenität. Sie müßen aber eine bakteriologisch besser angepaßte Definition erfahren.

2. Die atypischen Mykobakterien müssen als aktuelle oder potentielle für den Menschen pathogene Keime angesehen werden mit Gruppenvariationen in der Pathogenität. Sie sind weniger als der *M. tuberculosis* im Stande, eine fortschreitende Lungenerkrankung zu bewirken.

3. Unter unseren gesamten bekannten Fällen bilden die älteren männlichen Angehörigen der weißen Rasse die Gruppe mit der größten Zahl. Vorläufige Werte lassen vermuten, daß die farbige Rasse und besonders deren männliches Geschlecht den höheren Befall aufweist.

4. Männer, die in den ländlichen Bereichen des Südostens, geboren und dort die meiste Zeit ihres Lebens verbracht haben, sind am häufigsten betroffen von den nicht fotochromogenen Organismen.

5. Personen, bei denen sich herausstellte, daß sie diese Keime in sich tragen, gehören hauptsächlich zu der niedriggestellten Bevölkerungsklasse.

6. In unserem Material findet sich eine deutliche jahreszeitlich bedingte Schwankung im Auftreten und/oder der Ermittlung frisch erkannter Fälle.

7. Nach den zur Verfügung stehenden Angaben ist zu vermuten, daß eine familiäre Häufigkeit vorkommt, im Personen, die Anzeichen einer Exposition für diese Bakterien aufweisen; aber es wurden keine schlüssigen Beweise für eine Übertragung von Mensch zu Mensch kewonnen.

8. Der Fundort dieser Organismen bleibt unsicher; sie konnten von einer extra humanen Quelle gewonnen werden, möglicherweise dem Erdboden.

9. Die Entsteheung einer erkennbaren Erkrankung durch diese Bakterien könnte in Zusammenhang stehen mit früheren pulmonalen Veränderungen und einer herabgesetzten pulmonalen Resistenz.

10. Alle Erscheinungsformen dieser Infektionen bedürfen zusätzlicher Untersuchungen.

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Pulmonary Eosinophilic Granuloma*

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Eosinophilic granulomatous involvement of the pulmonary parenchyma has been a rare cause of diffuse pulmonary infiltration. This type of lesion, with histological proof of diagnosis, was first recorded in 1951 by Farinacci, Jeffrey, and Lackey[1] and has been reported in 24 cases in the English literature. Fifteen of the cases had involvement of the lungs without evidence of other organ involvement.

Eosinophilic granuloma of the lung fits into the reticuloendothelioses as a form of chronic or subacute disseminated histiocytosis. Lichtenstein suggested that in cases of "isolated" eosinophilic granuloma of the lung undetected lesions exist elsewhere in the body or subsequently develop.[2]

This paper will summarize the clinical, laboratory, and pathological aspects of all of the proved cases with lung involvement from the literature[1,4-15] and will report in detail six cases from this hospital (one previously reported).[3] Information collected from a total of 29 cases will be discussed.

Case Reports§

Case 1: A 42 year-old Caucasian man was admitted to this hospital in November, 1949, with a 20 pound weight loss, a nonproductive cough, acute severe upper respiratory infection, fever of 102° F., fatigue and anorexia. Physical examination revealed decreased breath sounds over both lung bases. The tuberculin skin test was positive. Chest x-ray films showed bilateral discrete pulmonary infiltration which was most prominent over the mid-lung fields.

Thoracotomy for lung biopsy revealed innumerable, scattered, discrete nodules of firm consistency and varying size and shape in the lung.

Symptoms gradually disappeared without specific therapy. He was discharged from the hospital in February, 1950. In August, 1950, chest x-ray film showed resolution of the infiltrate with residual fibrotic streaking and emphysema at the bases. In September, 1958, the chest x-ray film was unchanged.

Case 2: A 34 year-old Caucasian woman was admitted to the hospital in August, 1952, complaining of productive cough, afternoon temperature elevations and exertional dyspnea. Tuberculin and histoplasmin skin tests were positive. Chest x-ray films showed extensive bilateral pulmonary infiltration which was most prominent at the bases.

In October, 1952, thoracotomy revealed innumerable hard nodules varying in size from 2 mm. to 2 cm. in diameter throughout the lung parenchyma. Symptoms gradually subsided without therapy and she was discharged in November of 1952.

She has remained asymptomatic. Chest x-ray films taken in 1953 and 1958 show clearing of the infiltrate with some residual fibrosis at the bases.

Case 3: A 20 year-old Caucasian man was referred to this hospital in February of

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1958 with a diagnosis of eosinophilic granuloma of the lung. In 1956, he had had productive cough, rhinorrhea, right pneumothorax, bilateral pulmonary infiltrate, and eosinophilia of 5 per cent. In January of 1957, thoracotomy revealed multiple nodules throughout the entire lung.

His symptoms showed some spontaneous improvement and he was sent back to duty in June of 1957. However, he was never completely asymptomatic and, in February, 1958, he was admitted here for further studies. He was started on prednisone, 32 mg. per day, and this was gradually reduced to 10 mg. per day. The latter dose was continued for six months. Monthly chest x-ray films have shown no change in the pulmonary infiltrate. His symptoms are unchanged.

Case 4: A 19 year-old Caucasian man was admitted to the hospital in June, 1958, with history of weight loss, productive cough, left anterior chest pain, and postprandial emesis. Physical examination revealed palpable anterior cervical and supraclavicular lymph nodes. Laboratory studies showed a white blood count of 14,700 with

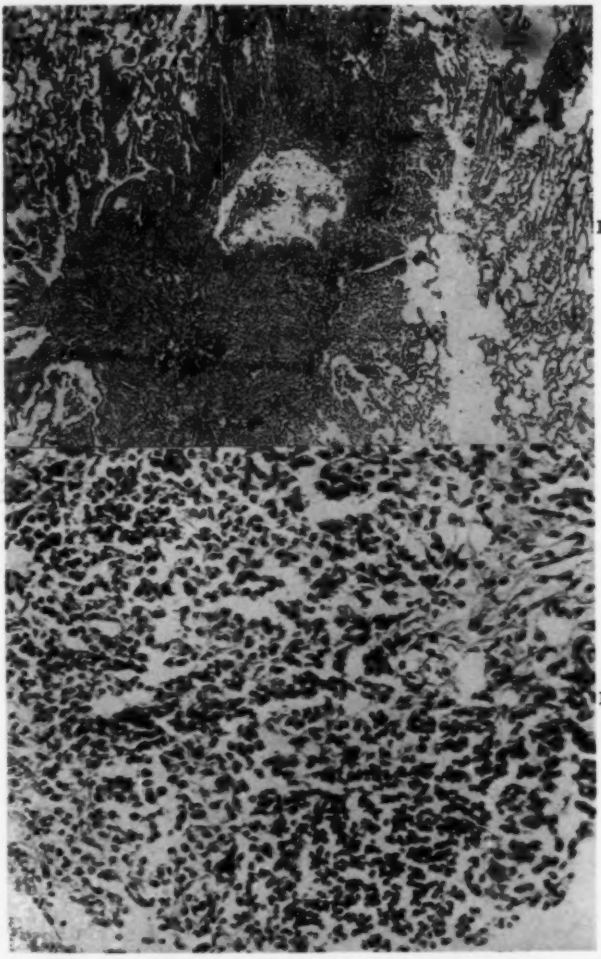

FIGURE 1

FIGURE 2

FIGURE 1: This is a photomicrograph showing a typical eosinophilic granulomatous nodule in the lung. Note in particular the normal appearance of the surrounding lung tissue.

FIGURE 2: This is a further magnification of a typical pulmonary eosinophilic granuloma. The pigment-laden and xanthomatous macrophages are prominent. Moderate numbers of eosinophils are scattered throughout the section.

4 per cent eosinophilia and sedimentation rate of 34 mm./hour. Chest x-ray films showed diffuse infiltrate in both lung fields. This was most marked in the hilar regions and the upper lung fields.

In July, 1958, thoracotomy revealed innumerable firm nodules throughout the lung. In October, 1958, he was asymptomatic and had regained some weight. His chest x-ray films showed no significant change from those taken at time of admission.

Case 5: A 36 year-old Caucasian man entered the hospital in July, 1956, with history of mild nonproductive cough and occasional left flank pain. Physical examination revealed tenderness over the 11th left rib posteriorly. Chest x-ray films showed an infiltrate symmetrically distributed throughout both lung fields with bilateral enlarged hilar lymph nodes. X-ray films of the ribs showed an area of increased density in the outer third of the 11th left rib. Eleventh rib biopsy was negative. He was discharged with a diagnosis of Boeck's sarcoid. During the next two years he noticed the onset of dyspnea, easy fatiguability, productive cough, and 38 pound weight loss. At the same time, chest x-ray films showed the disappearance of the enlarged hilar lymph nodes and an increase in the fibrotic streaking. He was readmitted to the hospital in September, 1958, because of progression of his symptoms. In October, 1958, exploratory thoracotomy revealed many small nodules throughout the lung. At present his condition remains unchanged.

Case 6: A 21 year-old Caucasian man was referred to this hospital in January, 1957, with a diagnosis of eosinophilic granuloma of the right femur.* Chest x-ray films showed a bilateral granular pulmonary infiltrate. While in the hospital he developed malaise, night sweats, low-grade fever, anorexia and had a 15 pound weight loss. In March, 1957, he underwent lung biopsy. There were numerous nodules up to 1.5 cm. in diameter scattered throughout the lung parenchyma.

Postoperative, his symptoms disappeared spontaneously and his chest x-ray films showed clearing. No specific therapy was given. He was returned to duty in June, 1957. In October, 1958, he was asymptomatic.

Pathology

The pathological picture in our patients varies little from that described by Auld.[5] There were no cysts or blebs in the lungs. The pleura was uninvolved. Innumerable firm gray or tan nodules, 1 mm. to 2 cm. in diameter, were noted throughout the lung parenchyma. The hilar lymph nodes were not grossly involved and therefore were not removed for biopsy.

Microscopically, the nodules consisted of histiocytes and eosinophils. The histiocytes were frequently laden with large amounts of brown pig-

*This case was previously reported by Williams, et al.[3]

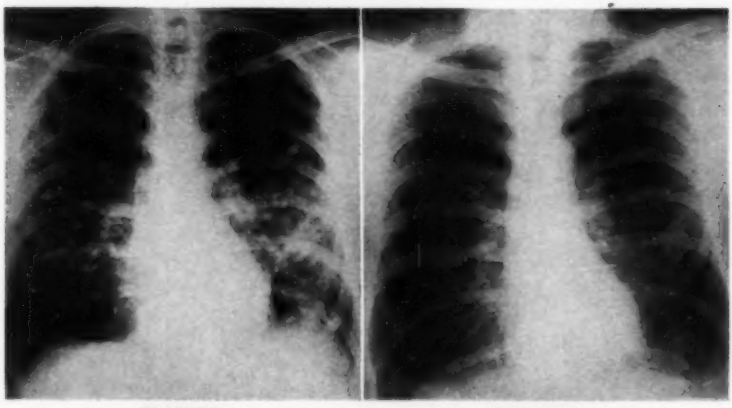

FIGURE 3 FIGURE 4

FIGURE 3: Chest film from Case 1 taken in 1950 during the acute phase of the disease. Note the discrete bilateral pulmonary infiltration which is most prominent over the mid-lung fields.

FIGURE 4: Chest film from Case 1 taken in 1957. At this time, the patient is completely asymptomatic. Note clearing of the infiltrate with residual fibrosis and a radiolucency suggestive of emphysema.

ment. The eosinophils were bilobed in most instances. There were occasional areas infiltrated with small round cells resembling plasma cells. Polymorphonuclear leucocytes and lymphocytes were present in small numbers. There were varying numbers of fibroblasts and amounts of fibrous tissue. Noncaseous central necrosis and multinucleated giant cells were occasionally present. The parenchyma around the lesions appeared overdistended and the alveolar septa showed thickening. Some interstitial fibrosis was present in every section. When involved, the arterioles showed intimal thickening and infiltration of adventitia and media with eosinophils and occasional small round cells. When the nodules involved a bronchiole there was infiltration of the bronchiolar wall with eosinophils, polymorphonuclear leucocytes, and small round cells. There was no particular area that was involved by the lesions more frequently than any other area. See Figures 1 and 2.

Sections and cultures were invariably negative for acid-fast bacilli and fungi.

Clinical and Laboratory Findings

The average age of the 29 patients with proved eosinophilic granuloma of the lung was 28½ with a range from 15 to 52 years. Four were women. One was a Negro.[15]

The symptoms are the same as those seen in other parenchymal lung diseases (Table 1). Physical examination was not remarkable except in those cases with emphysema or pneumothorax. Pneumothorax occurred in seven paients, in three of whom it was recurrent. Laboratory studies revealed a white blood cell count that was over 10,000 cells/cu. mm. in 12 of the patients. White cell differential counts showed from 4 to 15 per cent eosinophils in nine. The sedimentation rate was elevated in eight of the 11 patients in whom it was reported. Five of the 14 in whom serum proteins were reported had abnormal albumin to globulin ratios. Ten

TABLE 1 — SUMMARY OF SYMPTOMS

Symptom	Number of Patients Affected	
Cough	23	
non-productive		11
productive		12
Weight loss	13	
less than 15 lbs.		6
more than 15 lbs.		7
Dyspnea	10	
Chest pain	7	
Fatigue	7	
Pneumothorax	7	
single		4
recurrent		3
Temperature elevation	5	
less than 100° F.		2
more than 100° F.		3
Hemoptysis	3	
Night sweats	3	
Anorexia	2	
Weakness	2	
Emesis	1	
Malaise	1	
Asymptomatic	3	

TABLE 2 — PULMONARY FUNCTION STUDIES[1]

Case Number	Date	Age (yrs.)	Sex	Height (in.)	Weight (lbs.)	V.C.° (ml.)	V.C. % Pred.°°	I.C.° (ml.)	I.R.V.° (ml.)	E.R.V.° (ml.)	F.R.C.† (ml.)	R.V.† (ml.)	R.V. % Pred.°°	T.L.C.† (ml.)	T.L.C. % Pred.°°	F.R.C./T.L.C. X 100	R.V./T.L.C. X 100	M.B.C.†† (L./min.)	M.B.C. % Pred.°°	T.V.C.‡ % 1"	T.V.C.‡ % 2"	T.V.C.‡ % 3"	Air Velocity Index‡	Basal Ventilation° (L./M²/min.)	Tidal Volume° (ml.)	Oxygen Uptake° (ml./M²/min.)	Breathing Reserve ‡‡ (M.B.C.-Min Vent.) ÷ M.B.C. X 100	Vent. Equivalent§ (L./100 ml. O_2)	Walking Vent.†† (L./M²/min.)	Walking Index†† (W.V./M.B.C.)	Alveolar N_2† (%)	Compliance§§ (L./cm. H_2O)	Arterial Blood Gas, % O_2 Sat.¶ Rest	Exer.	100% O_2
I	1- 5-50	42	M	68	125	3900	100	2520	1950	.....	.....	.....	.....	.....	.....	...	...	82	78	...	...	.....	.....	5.9	570	144	88	2.4	....	...	.....	.....	...	...	.....
	9- 5-58	51	M	68	140	4590	122	3060	2160	1530	3540	2020	143	6610	128	54	31	117	105	67	79	88	0.95	4.4	900	174	93	2.5	10	16	1.76	.....	...	...	.....
II	9-13-58	40	F	66	143	3250	109	2760	2200	490	1970	1470	162	4720	121	42	31	111	122	81	88	94	1.05	6.2	560	134	90	4.5	13	20	0.92	.102	...	...	.....
III	3-13-58	21	M	69	125	2890	65	1870	1320	1020	2450	1530	137	4410	79	56	35	105	82	67	93	100	1.26	5.6	550	113	91	5.0	14	23	1.02	.....	...	...	.....
	8-12-58	21	M	69	125	2950	67	1860	1350	1090	2640	1620	146	4580	82	58	35	106	82	71	86	100	1.22	5.7	490	119	91	4.8	12	19	0.61	.072	97	99	100
IV	7-14-58	19	M	73	134	3500	74	2200	1570	1300	3160	1950	166	5450	92	58	36	113	81	83	94	94	0.99	3.8	630	156	94	2.1	15	29	0.94	.124	98	98	100
	10- 8-58	19	M	73	144	4240	90	2800	2100	1440	3410	1970	145	6210	102	55	32	114	81	74	91	91	0.82	4.5	700	167	93	2.7	10	9	1.22	.156	....	...	.....
V	8- 6-56	36	M	70	190	4230	98	3740	3110	490	1580	1090	101	5550	100	28	20	123	87	88	95	100	0.87	4.2	630	132	93	3.2	12	20	1.22	.....	....	...	.....
	4-22-58	38	M	70	170	4900	115	4030	3340	870	2580	1710	131	6610	120	39	26	117	90	75	80	89	0.69	3.8	690	114	93	3.0	12	19	1.42	.....	....	...	.....
	7-21-58	38	M	70	163	4710	110	3950	3280	760	3510	2750	210	7460	133	47	37	138	106	76	84	92	0.85	3.8	670	134	94	3.0	9	13	2.03	.172	88	90	97
VI	2-19-57	21	M	74	178	4150	87	3080	2500	1070	2960	1890	159	6050	102	49	31	161	103	93	98	100	1.13	5.4	580	178	93	3.1	7	9	0.44	.....	99	98	.....
	5- 2-57	21	M	74	178	4080	86	3140	2470	940	2590	1650	139	5730	96	45	29	134	86	86	95	98	0.88	4.2	670	126	93	3.4	7	11	0.75	.....	....	...	.....

[1]All volumes converted to BTPS except for oxygen uptake which is STPD.

°Closed circuit spirometry in the supine position.

°°Predicted values from Baldwin.[17]

†Modification of open circuit nitrogen washout method of Darling.[18]

††Method of Warring.[19,20]

‡Method of Gaensler.[21,22]

‡‡After Cournand and Richards.[23]

§Method of Matheson.[24]

§§Method of Frank.[25]

¶Standard Van Slyke manometric methods.

of 24 had positive tuberculin tests. Two of 22 had positive coccidioidin skin tests. Six of 22 had positive histoplasmin skin tests.

X-Ray Findings

There are two well-defined radiographic phases in the natural history of eosinophilic granulomatous involvement of the lung. Initially, there are localized areas of infiltration with poorly defined margins which coalesce to form large patchy areas of increased density. This phase terminates with involvement of all areas of the lung fields. Small radiolucent areas alternating with these infiltrations suggest associated emphysematous involvement; the composite radiographic appearance simulates a diffuse bronchial-interstitial pneumonitis. The hilar regions appear prominent, but close inspection reveals the density to be caused by the perihilar parenchymal infiltration rather than by nodal enlargement.

The second phase is a slow regression of these diffuse patchy infiltrates with the end result a diffuse but discrete infiltration. These nodular densities measure up to 5 mm. in diameter. A background of dense linear streaking suggests a diffuse interstitial fibrosis. At this later phase there is flattening of the diaphragms, increase in the retrosternal clear space, and a more horizontal configuration of the posterior ribs consistent with emphysematous changes. Fluoroscopy reveals a marked expiratory lag which is commonly seen in emphysematous chests. See Figures 3, 4, and 5.

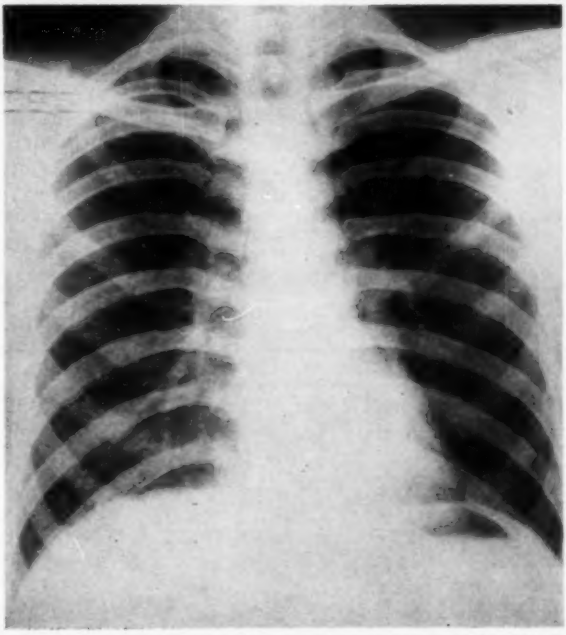

FIGURE 5: Chest film from Case 6 taken in January, 1957. Note the diffuse granular infiltration scattered throughout both lung fields. This film is typical of the appearance of eosinophilic granuloma in its early phases.

Pulmonary Function Studies (See Table 2)

Lung Volumes: The *vital capacity* was reduced below 80 per cent of the predicted values[17] in cases 3 and 4. Case 3 showed no change in vital capacity or other lung volume while on steroid therapy. Case 4 showed a rise in the vital capacity as he improved clinically. The *inspiratory capacity* of this group of patients ranged between 65 and 80 per cent of the vital capacity. The *functional residual capacity*[18] was elevated or borderline and the *residual volume* was elevated to over 140 per cent of the predicted values in every patient. (Note the rise in residual volume in case 5 from a normal value in 1956 to a definitely elevated one in 1958.) The *total lung capacity* was normal except in case 3 in whom it was reduced. The *residual volume to total lung capacity ratio* in this group of patients was elevated in every case above 30 per cent, which is our upper limit of normal.

Dynamic Air Exchange: The *maximum breathing capacity*[19] was normal. The *air velocity index*[20] was normal (with the possible exception of case 3). The *timed vital capacity*[21] showed minimal slowing. One case (3) showed increase in the timed vital capacity with bronchodilator drugs.

Respiratory Data: The *basal ventilation* was minimally elevated in cases 1, 2, 3, and 6. The average *tidal volume* was 640 ml. Case 1 showed the only abnormal tidal volume (900 ml.). The *respiratory rate* averaged 12 breaths/minute with a range of from nine to 19 breaths/minute. The *oxygen consumption* was within normal limits.

Breathing Reserve: The *breathing reserve*[22] at rest was above 90 per cent in all of these patients. The *ventilatory equivalent*[24] was elevated in all except cases 1 and 4. The *walking ventilation*[25] was elevated in cases 2, 3, 4, and 5.

Distribution of Gases: The *alveolar mixing index*[13] (alveolar nitrogen at the end of seven minutes of breathing 100 per cent oxygen) was below 2.5 per cent in all of these patients indicating absence of major inequalities in the ventilation of alveoli.

Compliance: The *lung compliance*[23] was 0.102, 0.072, and 0.172 L./cm. H_2O in cases 2, 3, and 5 respectively. Case 2 was asymptomatic and cases

TABLE 3 — SYMPTOMS AFTER TREATMENT

Type of Treatment	No. of Cases	Results of Treatment: Asympt-omatic	Im-proved	Un-changed	Pro-gressed	Not Stated
1. None	13	9	0	1	1	2
2. Treatment	16	7	4	3	2	0
a. X-Ray	4	2	1	1	0	0
b. X-ray + Steroids	3	1*	0	0	2	0
c. Steroids	6	1	3	2	0	0
d. Steroids + Antibiotics	1	1	0	0	0	0
+ Antituberculous Drugs	1	1*	0	0	0	0
e. Antibiotics	1	1*	0	0	0	0
TOTALS	29	16	4	4	3	2

*Asymptomatic before therapy was begun.

3 and 5 were symptomatic. Case 4 had a compliance of 0.124 L./cm. H_2O while symptomatic and 0.156 L./cm. H_2O after becoming asymptomatic.

Blood Gas Studies: Cases 3, 4, and 6 were normally saturated at rest and rose to over 98 per cent saturation with exercise. Cases 3 and 4 were also given 100 per cent oxygen for 10 minutes with resultant 100 per cent saturation. Case 5 was desaturated at rest and with exercise but was 97 per cent saturated when he inspired 100 per cent oxygen for 10 minutes. None of these four patients showed carbon dioxide retention.

Serial Studies: Two or more sets of studies were carried out on all except case 2. The interval between studies ranged from three months to eight years and eight months. Case 1 showed definite improvement in maximum breathing capacity and vital capacity over the eight year period between studies. Cases 3 and 6 showed little change over the period during which they were followed. Case 4 showed marked improvement in the three month period during which he became asymptomatic and began to gain weight. Case 5 was followed with repeated studies for over three years and showed a progressive rise in functional residual capacity, residual volume, total lung capacity, and residual volume/total lung capacity ratio. He also showed a progression in the slowing of the timed vital capacity.

Treatment

Twenty-four patients either received none or a single type of therapy, apparently depending upon the personal choice of the physician. X-ray therapy has been tried in a number of patients because of the dramatic response that is seen in eosinophilic granuloma of bone to low dosage irradiation. Steroid therapy has been tried in an attempt to prevent the pulmonary fibrosis which might otherwise develop. In only two of the five patients who received combinations of therapy were these combinations given because of failure of response to a previous regimen. A complete breakdown of the types of therapy and results is given in Tables 3 and 4.

Discussion

Our patients have shown an increase in the functional residual capacity, residual volume, and the residual volume/total lung capacity ratios as well as minimal slowing of the timed vital capacity. Compliance is reduced. The indices of dyspnea have been elevated in the patients with dyspnea. The spirograms have not shown any abnormalities. One patient was desaturated at rest and with exercise but was completely saturated with 100 per cent oxygen. These changes are parallel to those reported in one case by Mazzitello.[15]

TABLE 4 — X-RAY APPEARANCE AFTER TREATMENT

Type of Treatment	No. of Cases	Improved*	No Change	Worse	Not Stated
1. None	13	6	5	1	1
2. Treatment	16	9	7	0	0
a. X-Ray	4	3	1	0	0
b. X-Ray + Steroids	3	0	3	0	0
c. Steroids	6	3	3	0	0
d. Steroids					
+ Antibiotics	1	1	0	0	0
+ Antituberculous Drugs	1	1	0	0	0
e. Antibiotics	1	1	0	0	0
TOTALS	29	15	12	1	1

*None of the cases showed complete clearing.

Since Case 3 had restrictive pulmonary insufficiency with pulmonary overdistention at the age of 21, his prognosis must remain guarded. In Case 5 there was a gradual progression of symptoms and physiological deficits. Contrasting with these two patients are Cases 1 and 2 who have done well and have been followed eight years and six years respectively. The lack of more long term follow-up reports makes it impossible to draw any definite conclusion concerning the final outcome.

Among our own patients and those from the literature, 16 patients were asymptomatic at last report. Eleven have symptoms which appear to be of pulmonary origin of whom three have shown progressive pulmonary insufficiency. In two no follow-up was reported.

The treatment of eosinophilic granuloma is in doubt. This is due to the small number that has been reported and to the inability to correlate the clinical, x-ray and the pulmonary physiological status of the patients so that equivalent groups could be compared. In addition, there have been spontaneous remissions of symptoms and x-ray film changes in nine of the 13 patients who were followed without therapy. Lack of outstanding results with any particular therapy and the frequency of spontaneous remission may make it preferable to provide only symptomatic therapy as long as it is feasible clinically.

SUMMARY

1. Six cases of proved eosinophilic granuloma of the lungs are reported, including follow-ups of eight years and six years on two of them. Twenty-three additional cases from the literature are reviewed.

2. Pulmonary function studies showed the only consistent abnormality to be overdistention of the lungs. Lung compliance was reduced at some time during the course of the disease in three of four patients. Definite restrictive changes were demonstrated in one during the early stages of his disease.

3. Lack of rsponse to specific regimen of therapy in pulmonary eosinophilic granuloma is noted. Patients should be given the opportunity to undergo spontaneous remission.

ACKNOWLEDGEMENT: The authors wish to express their appreciation to Lt. William P. Sammons, MC, USN, of the Department of Radiology of the U. S. Naval Hospital, St. Albans, for his aid in interpreting the x-ray findings, and to Betty L. Vestal, Research Assistant, for her important contributions to this study.

RESUMEN

1. Se presentan seis casos demostrados de granuloma eosinófilo pulmonar incluyendo un seguimiento durante ocho años y de seis años en dos de ellos. Se revisan veintitres casos mas que se encontraron en la literatura.

2. Los estudios de la función pulmonar demostraron que la única anomalía consistente ha sido la excesiva distensión de los pulmones.

El rendimiento pulmonar se redujo alguna vez durante la enfermedad en tres de cuatro enfermos. Se encontraron trastornos consistentes en limitación en uno al principio de la enfermedad.

3. La falta de respuesta al régimen de tratamiento en el granuloma eosinófilo, es de notarse. Debe dárseles a estos enfermos la oportunidad de obtener una remisión espontánea.

RESUMÉ

1. Les auteurs rapportent six cas certains d granulome éosinophilique avec une surveillance de 8 ans et 6 ans portant sur deux d'entre eux. 23 cas supplémentaires recueillis dans la littérature sont passés en revue.

2. Les examens de la fonction pulmonaire montrèrent que la seule anomalie importante était l'hyperdilatation des poumons. L'expansion pulmonaire fut réduite à certains moments pendant l'évolution de l'affection chez trois malades sur quatre. Des altérations restrictives irréversibles furent mises en évidence dans un cas pendant le stade précoce de cette affection.

3. Les auteurs notent l'absence de tout traitement spécifique valuable pour le granulome pulmonaire éosinophilique. On ne peut espérer pour les malades que la possibilité d'une rémission spontanée.

ZUSAMMENFASSUNG

1. Bericht über 6 Fälle von bestätigtem eosinophilem Granulom der Lunge-einschlies slich einer Nachbeobachtungszeit von 8 bzw. 6 Jahren bei zwei von ihnen. 23 weitere Fälle aus der Literatur werden herangezogen.

2. Lungenfunfitionsproben zeigten, daß die einzig regelmässig auftretende Abnormalität in einer Überblähung der Lungen bestand. Das Lungenfassungsvermögen war irgenswann im Verlauf der Erkrankung bei drei von vier Patienten herabgesetzt. Wesentlich und auf die Dauer einschränkende Veränderungen ließen sich in einem Fall im Verlauf des Frühstadiums seiner Erkrankung nachweisen.

3. Bemerkenswert ist die Beobachtung einer fehlenden Reaktion auf spezielle therapeutische Maßnahmen bei dem pulmonalen, eosinophilen granülom. Patienten sollk gelegenheit gegsben werden, dis spontans Remission vor????

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Bovine Tuberculosis Eradication*

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One of the largest animal disease eradication programs ever to be inaugurated was begun more than 40 years ago.

To foster and continue to promote such an ambitious program took initiative, courage, and foresight on the part of State and Federal livestock sanitary officials, and leaders of livestock organizations. There were many who ridiculed the suggestion that all cattle in this country could be tested for tuberculosis.

During the period 1906 to 1917, Federal meat inspection records revealed that the percentage of cattle with lesions of tuberculosis more than doubled.

When the cooperative State-Federal eradication program was initiated in 1917, about 5 per cent of the cattle in this country were tuberculous. Tuberculosis was causing approximately 50,000 whole beef carcasses and an even greater number of swine carcasses to be condemned annually as unfit for human consumption. This was equivalent to a train load of live animals 20 miles long.

It is well known that these losses have been drastically reduced and all of us can, to some degree, visualize the human suffering and deaths due to *Mycobacterium bovis* that would be occurring today if bovine tuberculosis in its natural host had not been so effectively checked. On the other hand, we must admit that the goal of eradication has not been achieved.

Initially, the tuberculin test was almost entirely confined to valuable herds of purebred cattle under the accredited herd plan. Under this plan a certificate was issued to the herd owner when all cattle in the herd had passed repeated tuberculin tests covering a period of at least one year.

The accredited herd plan was soon integrated with area testing. Under this plan, all cattle owners in an area, usually a county, submitted their herds to be tuberculin tested by Federal, State and accredited (practicing) veterinarians.

Cattle positive to the tuberculin test were carefully identified and shipped to slaughter. Owners received indemnity payments from Federal and State governments to partially compensate them for the loss of these animals. Herds from which infected animals had been removed were placed under quarantine and the premises cleaned and disinfected.

When the incidence of bovine tuberculosis was found to be 0.5 per cent or less, individual counties were designated as "Modified Accredited Areas," and certificates were issued to each county as it gained this status. Before the end of 1940, all counties in the United States had achieved this goal.

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In the 12 year period following 1940, the number of reactors found throughout the United States continued to decrease until, in 1952, the disease reached a low point of 0.11 per cent of all cattle tested, or 11 in every 10,000.

What has happened since 1952? During 1953 and 1954, the percentage of reactors remained the same as in 1952. But in 1955 the number of reactors started to climb. Each year there was a gradual increase until, in 1959, a total of 23 of every 10,000 cattle tested were identified as reactors.

Why this increase in tuberculous cattle? In studying the problem it becomes obvious that several factors have contributed to this rise in infection.

In 1940, after the last State became a modified accredited area, livestock owners, veterinarians, and a great many others, in spite of warnings to the contrary, breathed a sigh of relief and concluded that the job was done. Obviously this wasn't true—it had only begun.

Interest in the eradication of bovine tuberculosis gradually dwindled. In spite of the determined and strenuous efforts of a few leaders, complacency progressively weakened the program and tuberculosis took a back seat as public interest in other animal diseases took over. Correspondingly, a decrease occurred in the allotment of funds for research and program activity.

The plain truth is that bovine tuberculosis is still with us, and we haven't won the fight or done our job until we've mopped up the last traces of it.

It is unfortunate, indeed, that severe outbreaks that practically eliminate some of our valuable herds must occur before we are awakened to the necessity for more concentrated action.

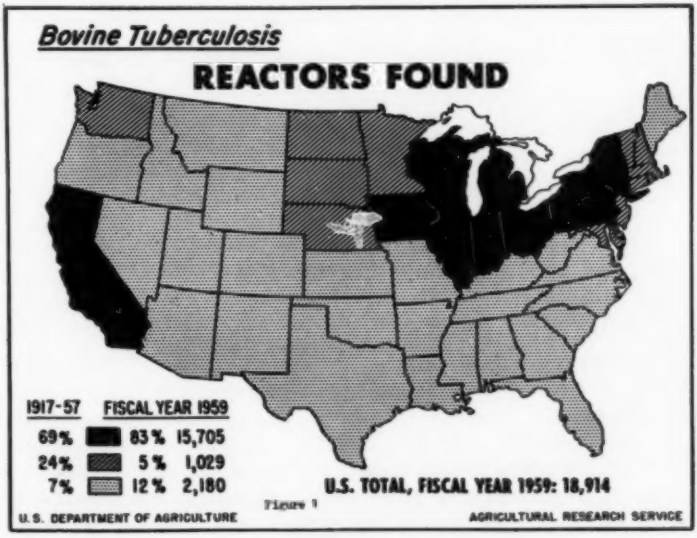

FIGURE 1

Certainly this is a major reason for the definite upsurge of program interest and activity that has taken place during the past few years. As a partial result of this increased interest, several conferences of national scope have been held in the past two years. These, too, have been helpful in revitalizing our efforts to eradicate tuberculosis.

Both the interest and enthusiasm felt by those attending these conferences were emphasized by the general agreement of those present on the immediate need for a vigorous and continued attack on tuberculosis which would lead to early eradication of the disease.

We are indebted to members of your organization who have been so helpful in stimulating our attack on tuberculosis in animals.

The themes that you have given this session on tuberculosis: Case-finding—Control—Eradication, are almost identical to a slogan that we have been using, Find it—Confine it—Eradicate it. This illustrates how closely the fundamental principles of tuberculosis eradication in humans parallels that of animals.

Effective case-finding is an essential part of tuberculosis eradication. We have depended upon the tuberculin test as the chief means of detecting tuberculous cattle. Over 400 million tuberculin tests have been made since the start of the program, and slightly more than 4 million reacting animals have been located and sent to slaughter.

Table 1 shows the results of tuberculin testing for fiscal year 1958. It will be noted that nearly 30 per cent of all reactors were found on retests applied to infected herds which involved less than 5 per cent of the total animals tested. The test results may be broken down into three major categories as shown in the Table.

TABLE 1

Reason for Test	Cattle Tested	Per cent of Total Cattle Tested	Reactors	Per cent of Total Reactors
Herd and area accreditation and reaccreditation	6,920,490	77.9	8,833	57.5
Retest of infected herds	426,423	4.8	4,516	29.4
All other tests	1,536,900	17.3	2,012	13.1
Totals	8,883,813	100	15,361	100

Another significant factor is the percentage of total reactors removed in certain States during the period from 1917 through 1957. There are as follows: 69 per cent in 9 states; 24 per cent in 13 states; and 7 per cent in 26 states.

The comparable figures for the same groups of states during fiscal year 1959 are: 83 per cent in 9 states (15,705 reactors); 5 per cent in 13 states (1,029 reactors); and 12 per cent in 26 states (2,180 reactors). These states are shown in Figure 1.

During fiscal year 1953 through 1959, 7,901 reactors were revealed as a result of tests after tracing to the herds of origin animals that were detected with lesions of tuberculosis on regular kill by veterinary meat inspectors. Of those reactors 5,538, or 70 per cent, were revealed in the same nine states where the highest percentage of total reactors were found in 1959.

In addition to routine tuberculin testing we have in recent years placed more and more emphasis on the importance of tracing infected and exposed animals. This is frequently referred to as "traceback" and may be divided into these three main categories:

1. Tracing to the herds of origin animals that show lesions of tuberculosis on regular meat inspection examination
2. Tracing the origin of animals that react to the tuberculin test
3. Follow-up of exposed animals

While these tracebacks are not always effective and complete, they are exceedingly helpful in locating centers of infection that might not otherwise be detected for an extended period. For example, an animal with generalized lesions of tuberculosis was found on regular kill at a slaughtering establishment. It was traced to a herd where 46 animals were tested and 16 reactors removed. Because of failure to obtain adequate records, or failure on the part of the owner to provide full information relative to sale of exposed animals, the investigation was terminated at that point.

Five months later, during a routine area test in another part of the State, a reactor was disclosed. This animal was traced from the farm to a dealer. The dealer's records showed he had previously sold this cow to another buyer who returned it the same month. The dealer had purchased the animal from the herd where the original 16 reactors were found.

Through registration papers, it was possible to identify this animal with still another farm, another dealer and finally the herd of origin. If a complete epidemiological study of the badly infected herd had been satisfactorily completed immediately after the herd test, it is reasonable to expect that the animal that had passed through the herd and later reacted would have been located much sooner. This would have prevented the spread of considerable potential infection.

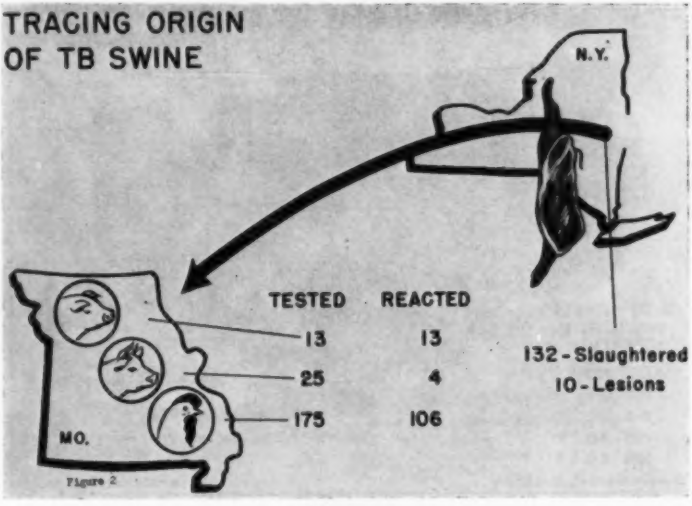

FIGURE 2

This serves to illustrate the necessity for adequate and complete records, as well as diligence in obtaining information that may be of value in locating tuberculous animals.

Successful tracing is dependent upon the cooperation of all principals involved—the accredited veterinarian, the owner, State and Federal disease eradication officials, stockyard and auction market operators, meat inspection personnel, cattle dealers, and others.

The importance of accurate and complete records cannot be overemphasized. Promptness in reporting, and in initiating and carrying out investigations, also determines to a large extent the success or failure of such projects. The permanent and uniform identification of cattle, together with an adequate system of records, are essential to effective and economical disease eradication.

The relationship of animal types of tuberculosis, and the necessity for a broad eradication program, are illustrated by several cases where the testing of swine that have shown lesions has resulted in locating premises with a high incidence of tuberculosis in cattle, swine, and poultry.

As shown in Figure 2, 10 swine from a lot of 132 were reported with tuberculous lesions in Albany, New York, in April, 1955.

Tracing these animals led to the testing of cattle, swine, and chickens on a farm in the Midwest with the following results: 25 cattle tested—4 reactors; 13 swine tested—13 reactors; 175 chickens tested—106 reactors.

At the present time, approximately 3 per cent of the swine slaughtered at establishments operating under Federal meat inspection reveal lesions of tuberculosis. Although this represents a considerable reduction in the incidence of infection since 1924, when 15 per cent were affected, it still involves a large number of swine.

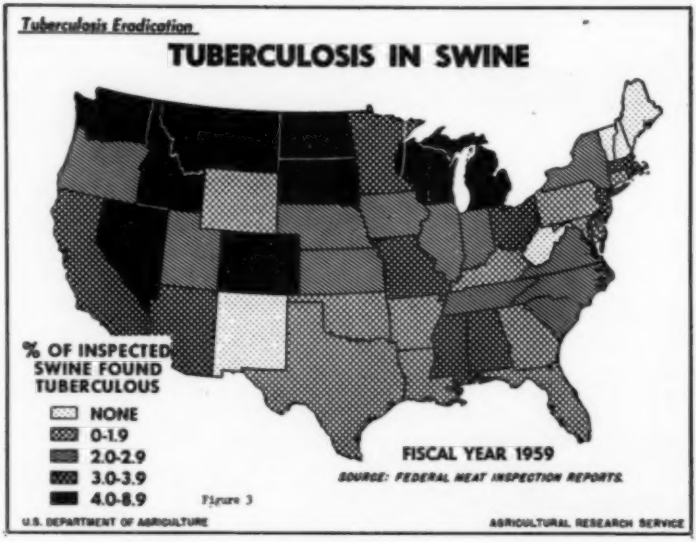

FIGURE 3

Data supplied by the Meat Inspection Division, ARS, revealed that 63,870,479 swine were inspected in fiscal year 1959 and 1,785,902 were retained because of tuberculosis. This is 2.78 per cent of those examined. Swine carcasses condemned and passed for cooking amounted to 9,263. The per cent of swine carcasses inspected in the various states and found to have tuberculosis have been placed in five groups as illustrated in Figure 3. A similar breakdown of data furnished by the Inspection Branch, Poultry Division, Agricultural Marketing Service, for tuberculosis in fowl is shown in Figure 4.

In considering these illustrations it should be pointed out that both swine and poultry may be shipped varying distances to slaughter and many lots may be slaughtered outside the areas in which the particular lot was raised.

These are some of the current problems that must be overcome in order to make further gains toward the goal of eradication. A major one, of course, involves the interspecies relationship of the various types of tuberculosis.

Another problem is the reactor which does not reveal any detectable gross lesions of tuberculosis on meat inspection examination. It is well known that early lesions of tuberculosis are very difficult to detect in a bovine animal, even on microscopic examination. Often it is impossible to examine all parts of an animal when meat inspection examination is made. This problem is also compounded by the fact that in some instances we are dealing with other types of tuberculosis.

It is interesting to note that the ratio of no-gross-lesion cases to the number of cattle tested remained rather steady until the country approached modified accredited status in 1940, with a slight decrease since that time. However, since 1940, the ratio of no-gross-lesion cases to

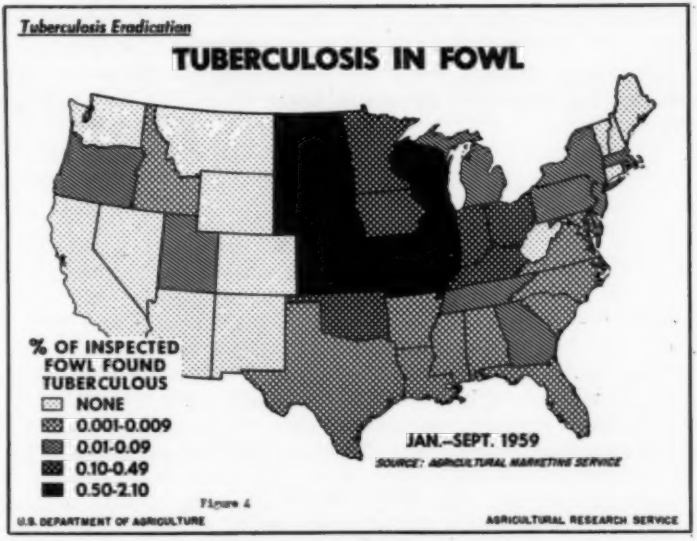

FIGURE 4

reactors slaughtered has increased steadily as the incidence of bovine tuberculosis has been reduced.

Since the over-all factors responsible for no-gross-lesion reactors tend to remain fairly constant, the reverse ratio of no-gross-lesion cases to total reactors is a condition that was expected with the decline in the rate of bovine tuberculosis. This problem, however, is one that demands continued study, especially from the standpoint of the effect of the various types of tuberculosis that involve our cattle population.

The human factor is another facet of the problem in dealing with various types of tuberculosis. Reduction of bovine tuberculosis in cattle can be directly correlated with the decrease in this type of tuberculosis affecting people. However, authentic information is not presently available to show how frequently the human type of the tubercle bacilli may cause cattle to respond to the tuberculin test.

We are frequently confronted with cases where tuberculosis in humans may be associated with the disease in cattle. Lack of thorough and complete laboratory examination for human cases as well as for cattle leaves many unanswered questions. With increased facilities for complete laboratory examinations of animal tissues, it may soon be possible to answer some of these pressing questions.

An impressive case occurring in New York State in 1954 centers around a herd owner who lost three complete herds due to tuberculosis before it was suspected that this owner was the possible source of infection. Examination of the patient's sputum revealed tubercle bacilli of the bovine variety.

I was most interested in the March 1960, issue of the "Public Health Counselor" which contained the program for this session. In reviewing the short articles by your members, I couldn't help but think how the statements made must be brought before the public, again and again. I'm sure that you have read the complete issue, but may I call to your attention a few statements by Drs. Novak, Anderson and Myers that are applicable to the eradication of tuberculosis from animals as well as man.

"Case finding, now that there are fewer than ever, must be pushed with great diligence."

"The whole problem to me still centers around the old and tried methods such as searching, searching, and searching for sources of infection —real detective work."

"Increased and continued vigilance seeking the source of infectious agents must be maintained. Men become complacent but not so the tubercle bacilli."

"The time is far overdue for an all-out simultaneous attack on all pathogenic forms of tubercle bacilli."

"We are still waiting for some person or some organization armed with the facts and with enough courage to cast aside much ado about nothing theories, personal opinion, speculation, etc., etc., to lead the long overdue movement necessary to eradicate all pathogenic types of tubercle bacilli."

CONCLUSIONS

It is most encouraging to note the increasing interest and support being given the bovine tuberculosis eradication program by the cooperating states. We are in an era of ever-increasing interest and enthusiasm in tuberculosis eradication activities, and

rightly so. A positive approach to the problem is necessary. With the continued support and spirit of cooperation on behalf of all people vitally concerned with this program, we can look to eradication as a reality and not merely a goal.

CONCLUSIONES

Es muy alentador notar el interés creciente y el apoyo prestado a los planes de erradicación de la tuberculosis bovina por los estados cooperantes. Estamos en una era de siempre mayor entusiasmo e interés en las actividades para erradicar la tuberculosis y con razón.

Se necesita atacar el problema de manera dinámica. Con el apoyo contínuo y el espíritu de cooperación de parte de todos los que están vitalmente afectados por este plan podemos contemplar en el futuro a la erradicación como una realidad y no como un simple objetivo.

RESUMÉ

Il est très encourageant de noter l'intérêt croissant et l'appui donné au programme d'éradication de la tuberculose bovine par la collaboration des différents états. Nous sommes dans une période d'intérêt passionné et d'enthousiasme pour les activités concernant l'éradication de la tuberculose. Une étude positive du problème est nécessaire. Grâce à l'appui continu et à l'esprit de coopération de la part de tous les gens concernés de façon vitale par ce programme, nous pouvons voir l'éradication comme une réalité et non simplement comme un but lointain.

SCHLUSSFOLGERUNGEN

Es ist in höchstem Maße förderlich, die sich verstärkende Anteilnahme und Unterstützung festzustellen, die dem Programm der Ausmerzung der Rindertuberkulose durch die mitwirkenden Länder zuteil wird. Wir befinden uns in einer Phase ständig zunehmenden Interesses und der Begeisterung hinsichtlich der Betätigung auf dem Gebiet der Beseitigung der Tuberkulose, und wir tun gut daran. Eine positive Einstellung diesem Problem gegenüber ist erforderlich. Unter der Voraussetzung einer kontinuierlichen Unterstützung und der Gesinnung einer Zusammenarbeit von Seiten aller Personen, für die dieses Problem äusserst lebenswichtig ist, können wir die Ausmerzung als eine Realität und nicht nur als ein Ziel ansprechen.

BENIGN ESOPHAGEAL TUMORS AND THEIR SURGICAL TREATMENT

The incidence of benign esophageal tumors is rather rare in comparison with other esophageal lesions. Until 1958, USSR literature reported 49 cases with benign esophageal tumors, 42 of which were subjected to surgery. Esophageal tumors could be distinguished as intraluminal and intramural tumors. Dense intraluminal tumors of the esophagus are mostly leiomyomas. The detailed analysis of the clinical data, roentgenoscopy and esophagoscopy make possible the operative diagnosis of these tumors. Surgery is recommended in treatment of benign esophageal tumors. Transthoracic approach has been used. Enucleation of the tumor is considered to be an operation of choice. We observed four patients with benign esophageal tumors (three leiomyomas, one fibroma); in three of them, the correct diagnosis was established preoperatively. All patients have been operated successfully. In three patients, enucleation was done; in one patient with a large leiomyoma in the gastroabdominal region, the resection of the lower esophagus and cardia with subsequent gastro-esophageal anastomosis have been performed.

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MEDICAL MORBIDITY IN A GENERAL HOSPITAL

"Degenerative" cardiovascular disease and chronic bronchial infection together accounted for 58 per cent of illness requiring admission to hospital.

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The Concentration of I^{131} in the Bronchial Tree after Oral Administration of Tagged CaI_2 and KI*

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Iodides are effective expectorants due to their rapid absorption from the gastrointestinal tract and subsequent diffusion through body membranes, including the bronchial mucous membrane.[1-3] Potassium iodide was first introduced in therapy. Its efficiency as an expectorant depends upon its iodide content. It has long been considered a safe and effective expectorant. A possible association, however, has been pointed out[3-6] between the ingestion of potassium and some abnormalities of cardiac action such as the production of hypertension, tachycardia, and multiple extrasystoles. These reports have stimulated recently the introduction of calcium iodide (CaI_2) as an alternate expectorant drug.

The use of calcium iodide would be favored by the fact that the iodine content in its molecule is 86.3 per cent by weight as compared to 76.4 per cent in the potassium iodide molecule and that no deleterious effect of calcium in the dosages which would normally be used are known.

The purpose of the present study is to compare the appearance and concentration of iodine in the bronchial secretions in man after the oral administration of equal doses of potassium iodide and calcium iodide. The thyroid uptake of iodine and the urinary excretion of iodine in each instance was also studied. Calcium iodide and potassium iodide solutions were prepared by I^{131}. The solution was of such concertation that 1 ml. of each contained 5 microcuries of I^{131}.

Methods

Twelve patients who were to be subjected to repeated bronchoscopy for various clinical indications were selected for the study. Each of them was studied in relation to both iodine salts.†† The two studies on each patient were separated by an interval of 14 days. An initial dose of 5 ml. of an aqueous solution of calcium iodide containing 25 microcuries of I^{131} was administered orally. At the stated interval of 14 days the same patients were given an equal dose of potassium iodide in aqueous solution which also contained 25 microcuries of I^{131}. Inasmuch as the half life of I^{131} is approximately eight days, the period of 14 days between the experimental studies was considered sufficient that only insignificant remnants of radioactive material remained in the body from the previous study.

Each oral administration was immediately followed by a bronchoscopic examination so that at an exact interval of 15 minutes after the admin-

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†National Institute of Cancer Trainee.
††Material supplied by Abbott Laboratories, Department of Radiopharmaceuticals, North Chicago, Illinois. Syrup Calcidrine®-KI and Syrup Calcidrine®-CaI_2.

istration a sample of bronchial secretion was aspirated from the patient. At the conclusion of the bronchoscopic examination as the instrument was removed, a small rubber catheter coated with an anesthetic jelly‡ was left in the bronchial lumen. This tube remained in place for four hours during which time bronchial secretions were aspirated at the end of 30 minutes, one, two, and four hours.

The I^{131} content of the bronchial sample was determined by comparing an aliquot of each specimen diluted to a constant volume with an aliquot of the material originally administered. Comparison was done by counting in a scintillation well under constant conditions. The results are expressed as a per cent of the administered dose but could be easily changed to milligrams of recovered iodine inasmuch as each patient received 151 mgm. of either potassium iodide or calcium iodide. The urinary excretion of I^{131} and the thyroid uptake were measured and calculated after 24 hours according to routine methods.

Results

Figure 1 shows the concentration of I^{131} expressed in per cent of total drug administered which appears in each ml. of sample recovered. The initial concentration is that which was present 15 minutes after administration of the drug when the first sample was taken, and subsequent concentrations are at 30 minutes, one, two, and four hours respectively thereafter.

Fifteen minutes after the administration of calcium iodide, each ml. of specimen aspirated contained 0.013 per cent of the total drug given. At 30 minutes the peak of the excretion curve was reached at a level of 0.042 per cent and the concentration climbed to 0.030, 0.014, and 0.006 per cent at one, two, and four hours respevtively.

‡Tronothane, Hydrochloride, Abbott.

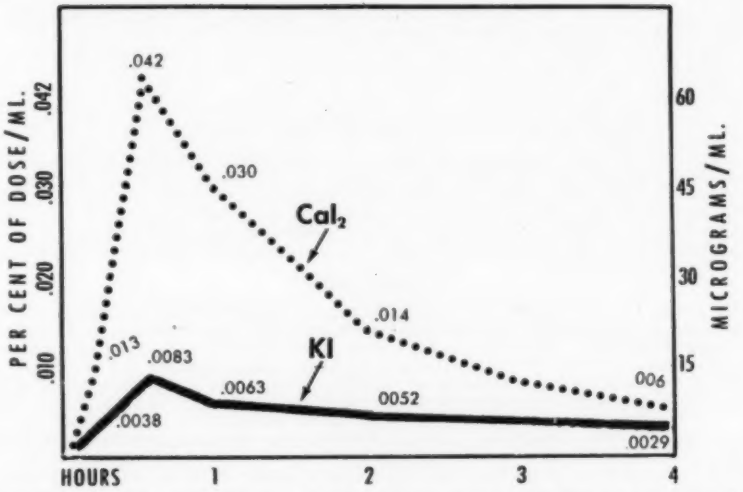

FIGURE 1: A summary of the results of giving 12 patients CaI_2 and KI. The graph gives the per cent of dose given as well as the micrograms of either CaI_2 or KI found in each ml. of secretion as a function of time following drug administration.

Radioactive iodine was present in bronchial secretions 15 minutes after its oral administration in a concentration of 0.0038 per cent of the total drug given. The highest level of concentration of radioactive iodine in the secretion was again reached at a period of 30 minutes at which time it was 0.0083 per cent and thereafter the drug concentrations declined to 0.0063, 0.0052, and 0.0029 per cent at one, two, and four hours respectively.

The figure shows that the curves representing the rate of secretion of iodine following the administration of the two drugs for a period of four hours measured at these intervals are similar in shape. Both peak levels were reached at the end of 30 minutes, and in both instances the drug appeared in the first sample taken at 15 minutes following administration. On the basis of the per cent of the total drug administered which was secreted in each ml. of aspirate, it has been found that calcium iodide secretion was 3.42, 5.07, 4.77, 2.69, and 2.07 times as concentrated at the intervals tested.

The urinary excretion of I^{131} in the first 25 hours following administration of each drug was measured. During this period 20.9 per cent of the total drug given was recovered after the administration of calcium iodide. After administering potassium iodide, the urinary drug excretion in 24 hours was 21.6 per cent of the total dose.

The thyroid uptake following the administration of calcium iodide was less than 1 per cent and following the administration of potassium iodide was between 0.5 and 1 per cent.

SUMMARY

A group of 12 patients having various bronchopulmonary diseases for which repeated bronchoscopy was indicated were given orally 5 ml. of aqueous solution containing radioactive calcium iodide and two weeks later the same group of patients received 5 ml. of solution containing an equal dose of iodine in the form of radioactive potassium iodide. The concentration of radioactive iodine in bronchial samples, the total urinary drug excretion, and the thyroid uptake were determined following the administration of radioactive iodine in each of the two forms.

In each instance, the excretion in detectable amounts in bronchial aspirates was found at a 15 minute period following administration. The excretion appeared to continue for a period of four hours on the basis of the continued detectability of radio-iodine in aspirates at that time. The highest level of concentration of radioactive iodine was found at an interval of 30 minutes after administration of each drug. Throughout the period of study a higher concentration in bronchial secretion was found after the administration of calcium iodide than after the administration of potassium iodide.

Total urinary drug excretion and thyroid uptake during the first 24 hours following the administration was not different following administration of the two drugs.

These studies suggest that calcium iodide administered orally results in a rate of bronchial secretion greater than that which follows the administration of potassium iodide. Calcium iodide may be a preferable expectorant drug on this basis, even apart from the possible dangers of the administration of potassium salt for the same purpose.

RESUMEN

Un grupo de 12 pacientes con afecciones broncorrespiratorias recibieron oralmente una dosis de 5 ml. de una solución acuosa conteniendo 25 microcuries de I^{131} en forma de yodudo cálcico, y dos semanas más tarde el mismo grupo recibió una dosis radioactiva igual de yoduro potósico. Después de la administración de yoduro cálcico o de yoduro potásico, se determinaron a diferentes intervalos la concentración de yodo radioactivo procedente de cada una de las sales, en las secreciones bronquiales durante la examinación broncoscópica o por medio de la aspiración endobronquial, así como la cantidad de yodo fijada a la glándula tiroidea y la excreción urinaria del mismo.

El yodo radioactivo procedente de ambas sales se detectó en el aspirado bronquial a los 15 minutos de su ingestión, persistiendo en el árbol bronquial durante 4 horas. La concentración máxima de yodo se obtuvo a los 30 minutos, tanto con el yoduro cálcico como con el yoduro potásico; no obstante, la curva de cncentración de yodo en el árbol bronquial durante las 4 primeras horas fué superior cuando se administró yoduro cálcico.

La excreción urinaria de yodo y la fijación yodada por la glándula tiroidea durante las primeras 24 horas fué idéntica con ambas sales. El resultado de este estudio comparativo demuestra que la administración de yoduro cálcico con fines expectorantes produce un aumento de secreción bronquial, superior al producido con la administración de yoduro potásico, por lo tanto el yoduro cálcico es superior al yoduro potásico, tanto por su acción expectorante como por su inocuidad.

RESUMÉ

Un groupe de 12 malades atteints d'affections broncho-pulmonaires variées pour lesquels des bronchoscopies répétées étaient indiquées, reçurent par la voie buccale 5 mml. d'une solution aqueuse contenant de l'iodure de calcium radioactif et deux semaines plus tard le même groupe de malades reçut 5 mml. d'une solution contenant une dose égale d'iode sous forme d'iodure de potassium radio-actif. La concentration de l'iode radio-actif dans les prélèvements bronchiques, l'excrétion urinaire globale du produit, et la fixation thyroïdiene furent déterminées après l'administration d'iode radio-actif sous chacune des deux formes.

Dans chaque cas, l'excrétion de quantités détectables dans les aspirations bronchiques fut trouvée après une période de 15 minutes suivant l'administration. L'excrétion semblait continuer pendant une période de quatre heures sur la base de la détection continue de l'iode radio-actif dans les produits d'aspiration à ce moment. Le taux le plus élevé de concentration d'iode radio-actif fut trouvé après 30 minutes suivant l'administration de chaque produit. Pendant le temps de l'étude, on trouva une concentration plus élevée dans la sécrétion bronchique après administration d'iodure de calcium qu'après administration d'iodure de potassium.

L'excrétion urinaire globale du produit et la fixation thyroïdienne pendant les premières 24 heures qui suivirent l'administration ne furent pas différentes après l'administration des deux produits.

Ces études suggèrent que l'iodure de calcium administré par voie buccale provoque un taux de sécrétion bronchique plus élevé que celui qui suit l'administration d'iodure de potassium. L'iodure de calcium peut être un produit facilitant mieux l'expectoration, préférable si l'on part de ces constatations, sans même teinr compte des dangers possibles par ailleurs quand on utilise le sel de potassium dans le même but.

ZUSAMMENFASSUNG

Eine Gruppe von 12 Kranken mit verschiedenartigen bronchopulmonalen Erkrankungen, bei denen eine wiederholte Bronchoskopie angezeigt war, wurde peroral mit 5 ccm einer wässrigen radioaktiven Jodcalzium enthaltenden Lösung behandelt; zwei Wochen später erhielt die gleiche Patientengruppe 5 ccm einer die gleiche Menge Jod in der Form von radioaktivem Jodkalium enthaltenden Flüssigkeit. Nach dieser Anwendung des radioaktiven Jodes in jeder der beiden Formen wurde seine Konzentration in dem gesammelten Bronchialsekret, die totale Ausscheidung des Mittels im Urin und die Konzentration in der Schilddrüse bestimmt.

In allen Fällen ergab sich die Ausscheidung in messbaren Mengen abgesaugten Bronchialsekretes in einem Zeitraum von 15 Minuten nach der Einnahme. Die Ausscheidung schien sich fortzusetzen während einer Zeitspanne von 4 Stunden auf der Grundlage fortlaufender Messebarkeit von radioaktivem Jod in dem zu diesem Augenblick abgesaugten Sekret. Die höchste Konzentration von radioaktivem Jod fand sich in einem Intervall von 30 Minuten nach der Einnahme des Mittels. Im Verlauf der ganzen Untersuchungsperiode fanden wir im Bronchialsekret eine höhere Konzentration nach der Verabfolgung von Jodcalzium als nach der Verabfolgung von Jodkalium.

Die Gesamtausscheidung des Mittels im Urin und die Konzentration in der Schilddrüse während der ersten 24 Stunden im Anschluss an die Einnahme ergab zwischen beiden Mitteln keinen Unterschied.

Diese Untersuchungen legen die Vermutung nahe, dass Jodcalzium bei peroraler Verwendung zu einer stärkeren Bronchialsekretion führt als dies der Fall ist nach der Gabe von Jodkalium. Jodcalzium wird daher auf dieser Bais als Expektorant vorzuziehen sein, ganz abgesehen von den möglichen Gefahren der Verwendung des Kaliumsalzes für den gleichen Zweck.

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Effect of Increasing Dosage of Streptomycin Sulfate on Serum Levels of Antimicrobially Active Drug*

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Microbiologic investigation of the prevention of emergence of mutant populations of tubercle bacilli resistant to either streptomycin or isoniazid demonstrated that adequate concentrations of each of these drugs should be simultaneously present in the culture media.[1] In tuberculous patients it was established empirically that such concentrations were at least 0.4 micrograms of isoniazid and 20 micrograms of streptomycin per milliliter of serum at six hours.[2,3,4]

Serum levels of antimicrobially-active streptomycin determined by microbiologic assay emphasized the fact that there were significant variations between individual patients.[2] These differences in serum concentrations have been attributed to variations in the rate of renal clearance of this drug and in the rate of absorption from the intramuscular depot into which the drug was injected.[2,5]

In order to establish whether low serum concentrations could be raised by increasing the dosage of streptomycin, the effect of doubling the loading dose of streptomycin sulfate from 10 to 20 milligrams per kilogram body weight was studied in a group of adult tuberculous patients.

Material and Methods

In order to eliminate the influence of pre-existing inflammatory reactions, which might have resulted from previous intramuscular injections, only those patients were selected who had not received streptomycin sulfate or any other intramuscular injection during the four-week period prior to the trial. Out of 170 adult tuberculous patients hospitalized at the time of the study, only six were found to satisfy this condition.

No other antimicrobial medication was given for two days before and during the period of the study. On the day of the test, venous blood samples were withdrawn from each patient before the administration of the drug. Thereafter, 10 milligrams of streptomycin sulfate per kilogram body weight was administered by the intramuscular route into the left gluteal region. A 20 gauge needle of standard length was used for the intramuscular injection. Six hours after the injection a second blood sample was withdrawn. Both samples were transferred to the laboratory for microbiologic assay of antimicrobially-active serum streptomycin.

Repeat studies were performed a week later on each of these patients under the same conditions after administering 20 milligrams of streptomycin sulfate per kilogram body weight by the intramuscular route into

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TABLE 1—EFFECT ON SERUM LEVEL OF INCREASING LOADING DOSE OF STREPTOMYCIN SULFATE FROM 10 mg. TO 20 mg. PER Kg. BODY WEIGHT at Six Hours After Intramuscular Injection

Patient	Serum Levels After 10 mg./kg.		Serum Levels After 20 mg./kg.	
	Zero hour level	Six hour level	Zero hour level	Six hour level
1	0 mcg./ml.	5.0 mcg./ml.	0 mcg./ml.	17.0 mcg./ml.
2	0 mcg./ml.	5.5 mcg./ml.	0 mcg./ml.	15.5 mcg./ml.
3	0 mcg./ml.	8.0 mcg./ml.	0 mcg./ml.	26.0 mcg./ml.
4	0 mcg./ml.	8.5 mcg./ml.	0 mcg./ml.	22.5 mcg./ml.
5	0 mcg./ml.	8.5 mcg./ml.	0 mcg./ml.	21.0 mcg./ml.
6	0 mcg./ml.	11.5 mcg./ml.	0 mcg./ml.	23.0 mcg./ml.

the right gluteal region. The patients were not aware of the various dosages of drug administered. The blood sample tubes were numbered from a table of random allocation so that bias of the laboratory technician was eliminated. The code was revealed only after the results of the microbiologic assays had been recorded.

The technique of microbiologic assay for biologically active serum streptomycin has been described elsewhere.[4] The test has been shown to be reproducible within the limits of error of the method: ±12 per cent.[2]

Results

The results of this investigation are presented in Table 1. It was evident that the patients had no measurable antimicrobially-active streptomycin in the serum prior to the administration of the drug.

The doubling of the loading dose of streptomycin from 10 milligrams to 20 milligrams per kilogram body weight produced in each patient an increase of the serum level of antimicrobially active drug. The mean increase was 176 per cent, which was shown statistically to be highly significant—$p<0.001$.

Comment

Two facts became evident from the results of this study. First, it was shown that by increasing the loading dose of streptomycin sulfate a higher serum level of antimicrobially active drug was achieved. The practical application of this fact is obvious: In those patients who do not achieve an adequate serum level after specific dosage of streptomycin sulfate, a higher level can be produced by increasing the amount of the administered drug. Conversely, in those patients who achieve an unnecessarily high level, the lowering of the dosage can still produce an adequate serum concentration with probable reduction of the undesirable toxic side effects.

Second, it is evident from the tabulated results that the per cent increase was not equal in different patients. A definite correlation was evident between the serum level achieved on 10 milligrams streptomycin sulfate per kilogram body weight and the increase after the administration of 20 milligrams per kilogram body weight: The lower the level was after 10 milligrams per kilogram, the higher was the per cent increase achieved by the doubling of the loading dose. However, the number of patients included in this study was too small to permit a definite conclusion from this apparent correlation.

SUMMARY

The effect of doubling the loading dose of streptomycin sulfate from 10 milligrams to 20 milligrams per kilogram body weight on the antimicrobially active drug was studied in six adult tuberculous patients. It was shown that by increasing the administered amount of streptomycin sulfate, an increase of the serum level of antimicrobially active drug was achieved.

RESUMEN

Se estudió cual era el resultado de doblar la dosis de sulfato de estreptomicina de 10 mg. por Kg. a 20 mg. en seis enfermos de tuberculosis activa. Se demostró que aumentando la dosis se obtenía un aumento de nivel antimicrobiano en el suero.

RESUMÉ

L'auteur a étudié chez six malades adultes atteints de tuberculose l'effet produit par l'augmentation de la dose de sulfate de streptomycine de 10 à 20 milligrammes de produit actif par kilogramme de poids corporel. Il est démontré que par l'accroissement de la dose de sulfate de streptomycine administré, il résulte une augmentation du taux du produit actif antimicrobien dans le sérum.

ZUSAMMENFASSUNG

Es wurde die Wirkung einer Verdoppelung der aktiven Dosis von Streptomyzin-Sulfat von 10 auf 20 mg pro Kilogramm Körpergewicht hinsichtlich der antimikrobiell aktiven Substanz bei 6 erwachsenen tuberkulösen Kranken untersucht. Dabei zeigte sich, daß durch eine Erhöhung der zugeführten Menge von Streptomyzin-Sulfat ein Anstieg des Blutspiegels der antimikrobiell aktiven Substanz erreicht wurde.

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EFFECT OF DRUGS ON THE RESPIRATORY RESPONSE TO CARBON DIOXIDE

There is no evidence to suggest that any commercially available potent narcotic produces significantly less respiratory depression than morphine when given in equi-analgesic doses.

Belliville, J. W., and Seed, J. C.: "Effect of Drugs on the Respiratory Response to Carbon Dioxide," *Anesthesiology*, 21:727, 1960.

SMALL PULMONARY ARTERIES STUDIED BY A NEW INJECTION METHOD

An analysis of ten cases of emphysema is presented and the results indicate that the reduction in the small arterial bed is much more than macroscopic appearance of the emphysema would suggest. Smaller vessels have disappeared while many of those remaining have thickened walls with narrowing of the lumen. This method measures the total reducing effect of these changes.

The findings in the differing groups of cardiac and respiratory disease are in accord with the view that elevation of capillary pressure or damage to the capillary bed acts as an immediate stimulus to restriction of the associated small arterial bed to protect the capillaries. Such reduction may be identified by measurement before it has produced changes that can be confidently observed by the microscope.

James, W. R. L., Owen, G. M., and Thomas, A. J.: "The Small Pulmonary Arteries Studied by a New Injection Method," *Brit. Heart J.*, XXII:695, 1960.

The Use of Atabrine (Quinacrine) in the Control of Recurrent Neoplastic Effusions

A PRELIMINARY REPORT*†

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In the course of a study of the intracellular distribution of Atabrine (quinacrine),[1] *in vitro* observations of the effects of the compound and its analogs on human and mouse tumor cells were made.[2] It was found that Atabrine has a cytotoxic action on a variety of tumor cells in tissue culture in concentration as low as M/50,000. When, however, the drug was administered to animals bearing a variety of experimental tumors, the results were disappointing with a single exception. Further investigations were carried out to determine why Atabrine, so destructive of tumor cells *in vitro*, was inactive against the same and other neoplasms *in vivo*. Studies of drug distribution in normal tissues and tumors revealed that the concentration attainable in the tumor cells without forbidding host toxicity was one-third to one-tenth that found necessary to produce an anti-tumor effect *in vitro*. Parallel experimental therapy of recurrent, x-ray-refractory, primary brain tumors in a small number of patients was similarly negative and again it was not possible with maximally tolerated doses given by mouth, intravenously or, even by intracarotid artery injection to achieve the concentration of drug found necessary *in vitro*.

It was found that when Atabrine was given intraperitoneally to mice with the Ehrlich ascites carcinoma, significant prolongation of survival time was achieved in six of eight experiments (Table 1). As can be seen from the results, the same doses of drug given subcutaneously were without effect. These observations provided further circumstantial evidence that Atabrine has a cytotoxic effect on tumor cells when they are exposed to a sufficient concentration of the drug. From this, it was thought that the compound might be useful in the control of neoplastic effusions by direct instillation into the involved cavities and the experience to be summarized here supports this hypothesis.

Materials and Methods

Thirty-one patients were selected for evaluation of the use of Atabrine in the control of effusions. The following criteria were rigidly followed:

The diagnosis of neoplastic effusion was confirmed by cytological study of the sediment.

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††Established Investigator, Health Research Council, City of New York.

Evidence was obtained in every instance that the effusion was symptomatic and was recurrent with sufficient frequency so that the effect of the drug on the rate of reaccumulation could be examined.

Twenty-one patients with recurrent pleural effusions secondary to metastasis from carcinomas of the breast and lung, lymphoma and mesothelioma, and ten patients with recurrent ascites secondary to ovarian, colon, pancreas, stomach and breast carcinomas and mesotheliomas were evaluated.

The Atabrine used was available as the hydrochloride salt* in sterile ampules containing 200 mg. Various dosage regimens were tried as will be indicated in the individual case histories but at the present time the following procedure is recommended:

For pleural effusions, a thoracentesis is performed removing approximately two-thirds of the fluid.

200 mg. of the Atabrine hydrochloride are dissolved in 10 ml. of sterile water. This solution has a pH of 5.5.

The drug solution is injected directly into the remaining pool of pleural fluid.

Depending upon the presence and severity of the reaction (*vide infra*) 200 - 400 mg. of Atabrine are injected on subsequent days into

*We wish to acknowledge with thanks the supply of Atabrine brand of quinacrine, Winthrop Laboratories, New York.

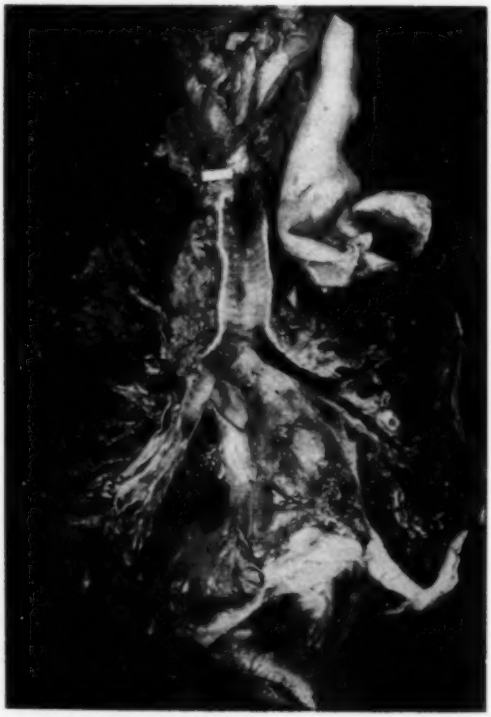

FIGURE 1—Case 1: Note the markedly thickened and constricting pleura on the left.

TABLE 1 — EFFECT OF ATABRINE ON EHRLICH ASCITES CARCINOMA

Expt. No.	Rx	Route	Dosage mg/kg/day	No. of Animals	Mean Survival (Days)	S.E.* (Days)	Probable chance occurrence of difference between control and treated groups (per cent)**
450	Saline	IP		16	10.7	1.7	
	Drug	IP	150 x 3***	18	21.2	2.9	0.2
455	Saline	IP		18	15.6	1.9	
	Drug	IP	150 x 3***	17	18.2	1.3	27
408	Saline	IP		14	13.1	1.0	
	Drug	IP	125 x 3	14	22.2	3.5	1.2
413	Saline	IP		14	8.9	0.8	
	Drug	IP	125 x 3	14	16.9	1.2	0.000002
419	Saline	IP		14	11.9	0.9	
	Drug	IP	125 x 3	14	16.6	0.8	0.01
432	Saline	IP		18	15.1	1.4	
	Drug	IP	100 x 3	18	22.8	2.9	1.6
	Drug	SC	100 x 3	15	22.7	3.7	2.8
437	Saline	IP		17	13.0	0.9	
	Drug	IP	100 x 3	18	16.1	0.6	0.4
	Drug	SC	100 x 3	18	12.2	0.8	>50
442	Saline	IP		17	13.2	1.2	
	Drug	IP	100 x 3	18	13.4	1.5	>50
	Drug	SC	100 x 3	18	16.3	1.8	16

*S.E.=Standard error of the mean

**A value of 2 per cent or less indicates a statistically significant difference.

***Given in two daily doses of 75 mg/kg about eight hours apart.

the pleural cavity until a total dose of 1000-2000 mg. of the drug has been given. It is usually unnecessary to repeat a thoracentesis on the succeeding days of drug administration and the Atabrine can be injected into the pleural fluid with a 21 needle following procaine instillation of the skin and subcutaneous tissues.

In the management of ascites, a paracentesis is performed leaving sufficient fluid within the peritoneal cavity so that the Atabrine

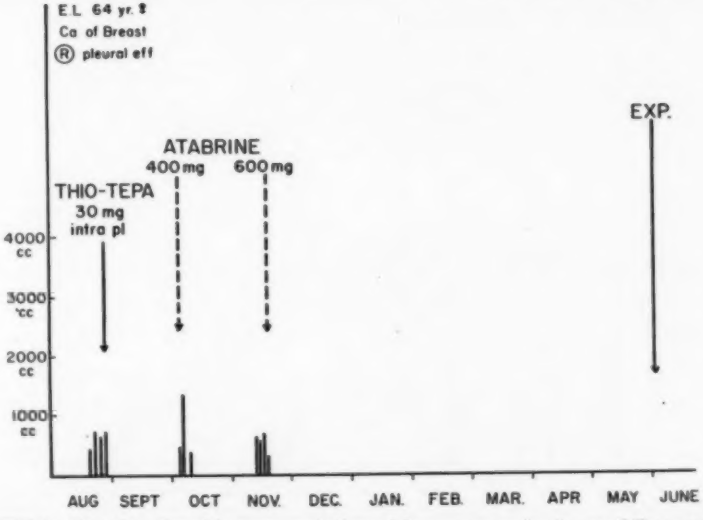

FIGURE 2—Case 6: Graphic representation of frequency and volume of thoracenteses before and after Atabrine.

can be injected readily into the residual pool. An initial dose of 400 mg. in 20 ml. of water is injected and this dose or up to 800 mg. of the drug is repeated on succeeding days until 3 to 4 grams has been given. The size of the dosage given on days after the first administration depends upon the reaction of the patient to the initial dose.

As has been indicated above, the hydrochloride salt of Atabrine in water has a pH of 5.5. When this is administered in neoplastic effusions, the buffering activity present rapidly neutralizes the salt. Thus it has been observed that when doses as great as 800 mg. are given, there was no detectable change in the pH of the effusion, even within a matter of minutes after the instillation.

Results

Table 2 summarizes the results obtained in the treatment of effusions in 31 patients. Among the 31 selected for management of recurrent effusions, 10 have been inadequately followed and five had treatment complicated by other therapy making them unsatisfactory for evaluation. The large number of inadequately followed patients reflects the fact that nine died less than one month after the onset of Atabrine therapy. The size of this group indicates the large proportion of far advanced problems of neoplastic diseases in this series. Further, the requirement that a recurrence of the effusion be demonstrated curtails the number of patients to be studied. Five received another therapeutic measure which invalidated the evaluation of the Atabrine regimen (prednisone for the control of hemolytic anemia, triethylene thiophoshoramide intrapleurally, mediastinal radiotherapy). There was one complete failure

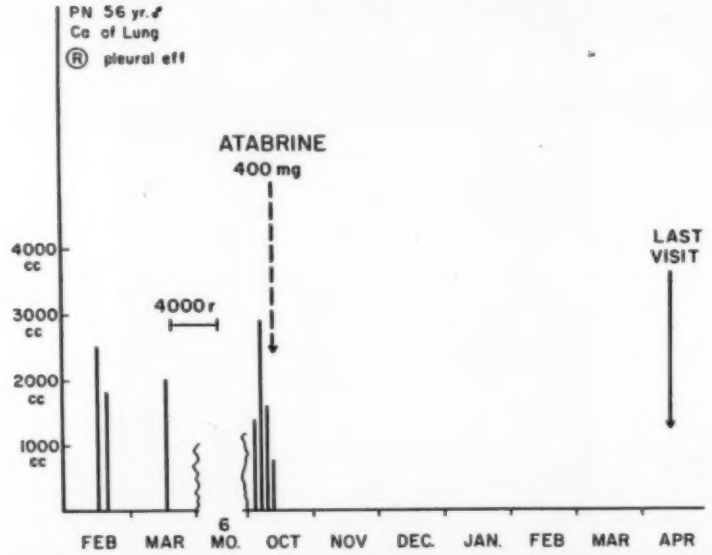

FIGURE 3—Case 14: Graphic representation of course of pleural effusion before and after Atabrine.

TABLE 2 — SUMMARY OF ATABRINE-TREATED NEOPLASTIC EFFUSIONS

Location of Effusions	Total No.	Inadequately Followed	Complicated by Other Rx	Failure	Effective Control	
Pleural	21	8	3	1	Breast	5
					Lung	3
					LSA	1
Peritoneal	10	2	2	1	Ovarian	3
					Colon	1
					Breast	1

in a patient with a peritoneal and pleural mesothelioma with free connection between the ascites and the pleural effusion.

Table 3 presents all patients studied with details regarding their courses before and after treatment. Representative case histories follow.

Case 1: J.W. In this case of lymphoblastic lymphosarcoma, left pleural effusion positive for tumor cells developed in July, 1956 and 11 thoracenteses were required over a three-month interval. Atabrine was injected intrapleurally beginning October, 1956 and no further thoracenteses were required on the left side during the remainder of the patient's course of 13 months. There was a febrile (up to 102° F.) response to the Atabrine instillation which gradually subsided over a 10-day period. Subsequently, chest radiographs showed complete opacification of the left hemothorax. Two months before death, right pleural effusion developed from which tumor cells were not recovered. It was presumed that this was a manifestation of lymphatic obstruction in the mediastinum.

At necropsy there was generalized lymphosarcoma. A massive right pleural effusion was present, but without tumor involvement. The left pleural cavity which had received the Atabrine was obliterated by dense adhesions (Figure 1). There was one loculated pocket of fluid containing 200 ml. of fluid.

Case 5: C. V. This patient had a large fungating tumor of the breast, which had increased progressively for one year. She also had a right pleural effusion positive for tumor cells. Local radiotherapy controlled the breast tumor but recurrent pleural effusion became an increasing problem. She received a single 400 mg. injection of Atabrine with febrile response to 101° F. for 24 hours. During the remaining six months of her

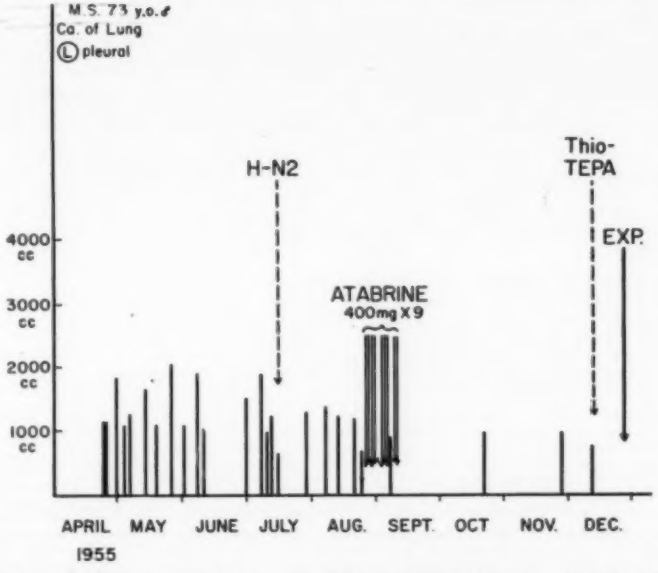

FIGURE 4—Case 17: Course of pleural effusion before and after Atabrine. HN_2 was administered intravenously.

TABLE 3 — THE EFFECT OF ATABRINE ON NEOPLASTIC EFFUSIONS

Case No.	Diagnosis	Before Rx: Duration of Effusion (Months)	Before Rx: No. of Taps	Before Rx: Vol. (L.)	Before Rx: Atabrine Dose (mg. x days)	After Rx: Total Time (Months)	After Rx: No. of Taps	After Rx: Vol. (L.)	After Rx: Toxicity	Remarks
A. PLEURAL										
1	Lymphoma	4	11	21.0	400 mg x 4	13	0	0	Fever	Effective cont:
2	Lymphoma	R3	11	12.0	400 mg x 6	6	1	.1	Pain	Patient received
		L3	7	5.7	400 mg x 5	6	0	0	Fever	iastinal radiotherapy and prednisone after Atabrine; unsuitable for evaluation
3	Hodgkins	R9	4	4.8	400 mg x 1	.5	1	.5	Fever	Coronary occlusion;
		L9	7	4.7	400 mg x 1	.5	1	.1	Fever	inadequate time for evaluation
4	Lymphoma	1	6	9.0	400 mg x 1	.25	0	0	None	Terminal case; inadequate time for evaluation
5	Ca. Breast	2	5	2.1	400 mg x 1	6	0	0	Fever	Effective control
6	Ca. Breast	3	11	8.0	400 mg x 1 600 mg x 1	6	0	0	Pain Atelectasis	Effective control
7	Ca. Breast	2	11	4.7	400 mg x 2	13	1	.25	None	Intrapl. Thiotepa given; unsuitable for evaluation
8	Ca. Breast	2 wks	3	2.3	200 mg x 2	12	1	.25	Pain Fever	Effective control
9	Ca. Breast	2	6	4.0	400 mg x 2	.75	1	.5	None	Terminal case; inadequate time for evaluation
10	Ca. Breast	3	8	6.0	400 mg x 4	.1	0	0	Fever	Terminal case; inadequate time for evaluation
11	Ca. Breast	1	3	1.0	400 mg x 1	2	1	.7	None	Lost to follow-up
12	Ca. Breast	1	4	2.5	200 mg x 2	5	3	1.2	Pain Fever	Effective control
13	Ca. Breast	6	6	8.5	200 mg x 1 400 mg x 1	8	1	.3	Pain Fever	Qualified success
14	Ca. Lung	8	16	13.5	400 mg x 1	26	3	0	Fever	Effective control
15	Ca. Lung	1	6	4.8	400 mg x 1	3.5	3	0	Pain Fever	Effective control
16	Ca. Lung	2	8	12.0	400 mg x 5	.5	2	3.8	None	Terminal case; inadequate time for evaluation
17	Ca. Lung	5	21	25.0	400 mg x 9	4	3	2.5	Fever Pain Atelectasis	Effective control
18	Mesothelioma	1	7	6.5	600 mg x 1 400 mg x 1	5	9	6.5	None	Failure; patient had proven communication between the 3 serous cavities
19	Melanoma	2	8	1.0	400 mg x 2	.5	0	0	Fever	Terminal case; inadequate time for evaluation
20	Ca. ?	1 wk	2	3.8	400 mg x 1	1	0	0	None	Inadequate time for evaluation
21	Ca. ?	1	9	6.0	800 mg x 1 400 mg x 1 200 mg x 1	5	0	0	Fever	X-ray therapy to mediastinum following Atabrine; unsuitable for evaluation
B. PERITONEAL										
22	Ca. Ovary	5	10	52.0	600 mg x 1 800 mg x 1 1000 mg x 2	1	0	0	Fever	Inadequate time for evaluation
23	Ca. Ovary	3	8	24.0	1000 mg x 3	3.5	2	3.0	Pain Nausea	Effective control
24	Ca. Ovary	5	5	18.0	200 mg x 1 600 mg x 4	2	0	0	Pain	Effective control
25	Ca. Ovary	1	3	15.0	600 mg x 1 800 mg x 1 1000 mg x 2	2	0	0	Pain Nausea Abdominal resistance	Effective control
26	Ca. Breast	3	3	18.0	1000 mg x 1	6	0	0	Pain	Two courses with
		2	1	2.0	1000 mg x 1	7	0	0	Fever	effective partial control. Radiotherapy given after first course
27	Mesothelioma	4	4	8.5	1000 mg x 3	2	1	2.8	None	Failure; proven communication between 3 cavities
28	Mesothelioma	2	3?	3.0?	600 mg x 4 1000 mg x 1	3	6	2.0	None	Other local and systemic chemotherapy given simultaneously; unsuitable for evaluation
29	Ca. Colon	4	3	21.0	800 mg x 1 1000 mg x 1	2	0	0	Pain	Effective control
30	Ca. Stomach	1	2	6.0	100 mg x 1	.1	0	0	None	Terminal case
31	Ca. Pancreas	1	3	7.0	600 mg x 3	.25	0	0	None	Terminal case

life, no further thoracenteses were required. Preterminally she developed radiological evidence of effusion again, but no fluid could be obtained by thoracentesis. She died a respiratory death secondary to lymphatic distribution of tumor within the lung parenchyma. Autopsy was not performed.

Case 6: E.L. Radical mastectomies were performed on the left in 1943 and on the right in 1951 for carcinoma of the breast. In April, 1957, right pleural effusion developed which was rapidly recurrent by August. Intrapleural thioTEPA had only a transient effect as did a single dose of 400 mg. of Atabrine six weeks later. In November, another 600 mg. of Atabrine was injected intrapleurally with control of the effusion during the remaining seven months of her life. (Figure 2) At autopsy, the right pleural cavity was obliterated and there was some compression of the lung by the contracted scar tissue.

Case 8: R.R. Inoperable carcinoma of the breast was documented with tumor mass biopsy and positive internal mammary nodes. Following radiotherapy, she remained asymptomatic for 18 months, when left pleural effusion appeared requiring three thoracenteses over a two-week period. Two single doses of 200 mg. of Atabrine were instilled on consecutive days producing fever to 102° F. and a short episode of pleuritic pain. Shortly after this therapy, 250 cc. of fluid were removed from the chest. No further thoracenteses were required during the remaining 12 months of the patient's life.

Case 13: R.G. A carcinoma of the breast was treated in 1950 by radical mastectomy and postoperative radiotherapy. Gradual progressive carcinoma *en cuirasse* since 1955 was extensively treated with radiotherapy and hormones. Right pleural effusion six months prior to therapy was positive for tumor cells at thoracentesis November, 1958 (2L). Four additional thoracenteses were performed during April and May, the last of which was complicated by an induced pneumothorax. Despite this, 200 mg. Atabrine was instilled with a temperature rise to 104° F. and local pain. Another dose of 400 mg. Atabrine was instilled six days later, with spiking fever up to 104° F. for several days. Cultures were negative. Local pain continued and also signs of pneumothorax. The pain which was considered to be caused by adhesions slowly subsided over a six-week period.

No further thoracentesis was required during the remaining 8 months of the patient's life and dyspnea improved. At necropsy the right pleural cavity was obstructed. This is considered a successful control of recurrent effusion, but only a qualified clinical success due to the protracted fever, local pain and dyspnea. It is concluded that Atabrine should not be used when spontaneous or induced pneumothorax is present.

Case 14: P.N. Carcinoma of the lung with right pleural effusion was the first clinical manifestation which was satisfactorily controlled by radiotherapy. Six months later, fluid in the same cavity reaccumulated requiring four thoracenteses in one week for a total of 6400 cc. A single dose of 400 mg. of Atabrine was instilled followed by a febrile episode to 103° F. lasting three days. Subsequently, three thoracenteses were performed because of radiological evidence of persisting effusion. No fluid, however, was obtained and 10 months later no clinical or radiological change was evident (Figure 3). The patient remains asymptomatic 26 months after therapy and x-ray of the chest shows a marked pleural thickening on the right.

Case 15: D.J. Carcinoma of the lung was diagnosed four months prior to the appearance of right pleural effusion. Six thoracenteses were performed in three weeks before the administration of a single 400 mg. dose of Atabrine. Although some loculated fluid remained, no further reaccumulation was noted for three and one-half months, when the patient expired from widespread metastatic disease. Autopsy was not performed.

Case 17: M.S. The patient had a left pleural effusion secondary to carcinoma of the lung. Short-lasting palliation was achieved with radiation therapy. Subsequently, systemic chemotherapy with nitrogen mustard failed to control the disease and 21 thoracenteses were performed over a five-month period. Doses of 400 mg. of Atabrine were repeated nine times over three weeks. Each instillation was followed by a 24-hour febrile episode; pleuritic pain occurred in some instances and some degree of lung collapse persisted following pneumothorax. A complicated cardiac arrhythmia developed concomitantly.

During four months of survival a marked decrease in the rate of fluid accumulations was noted although three additional thoracenteses became necessary. Terminally, pleural effusion developed in the opposite chest and local thioTEPA was used with no appreciable results. Permission for autopsy was not granted (Figure 4).

Case 18 and 27: F.Mc. This patient had a malignant mesothelioma involving both pleural and peritoneal cavities producing massive effusions. Free circulation from one cavity to another was demonstrated by recovering Atabrine at equal concentrations in all effusions after instillation in only one of them. The right pleural cavity was treated with 1000 mg. of Atabrine and the peritoneal cavity with 3000 mg. The left pleural space was left as an untreated control.

Neither the Atabrine therapy nor later external radiation therapy to both pleurae affected significantly the massive production of fluid and this case has been catalogued as a failure.

Of interest, however, was the striking difference between treated and untreated pleurae on postmortem examination. The first showed marked fibrosis with complete absence of tumor on the surface with small foci growing subpleurally towards the lung parenchyma. The untreated pleura showed extensive neoplastic involvement. (Figures 5 and 6)

Case 23: L.C. Documented carcinoma of the ovary was treated with radiation therapy and asymptomatic for the following six months, when massive ascites developed which failed to respond to intraperitoneal instillation of radioactive colloidal gold (Au^{198}). Two months later, after 24 liters of ascites were obtained, 3000 mg. of Atabrine was given intraperitoneally in equally divided doses on three consecutive days. Nausea and abdominal resistance developed. She died three and one half months later from widespread carcinomatosis. During this time only two paracenteses were performed.

Case 24: P.C. Advanced ovarian carcinoma was treated with radiation therapy with no significant effect; rapidly accumulating ascites developed which intravenous thio-TEPA failed to control. Two months later Atabrine was given intraperitoneally for a total dose of 2600 mg. over a two-week period. After this no fluid was obtained in two further attempts and she expired two months later after a second laparotomy with findings of a "plastic peritonitis" with no fluid.

Case 25: A.C. Right pleural effusion and massive ascites secondary to metastatic disease from ovarian carcinoma was treated originally with radiation therapy to the pelvis. In addition, she received 3000 r. to the right chest with decrease in the pleural effusion. Subsequently, after 15 liters of ascites were obtained in one month, she received intraperitoneal Atabrine on consecutive days as follows: 600 mg.; 800 mg.; 1000 mg.; and 1000 mg. Nausea, abdominal tenderness and resistance developed after the last dose, subsiding after approximately 36 hours. No further reaccumulation of ascitic fluid was noted until death, two months after therapy. At postmortem, neither fluid nor gross evidence of neoplastic disease was found in the abdomen, while pleural involvement with effusion was present.

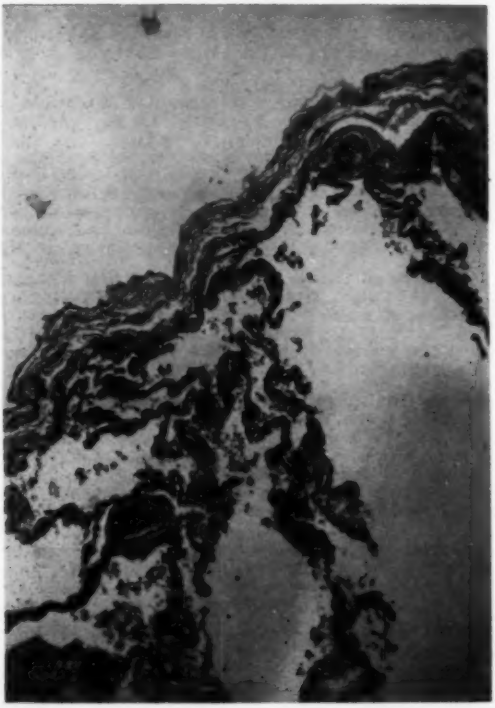

FIGURE 5: Photomicrograph of a normal pleural surface x300.

Since this manuscript was submitted, 10 additional patients have been treated with intracavitary Atabrine. Of these, five could not be evaluated since they died less than a month after treatment. In the other five patients, complete control of the effusion was achieved. These included two with carcinoma of the breast (3 and 6 months without recurrence) and one each with carcinoma of the ovary (12 months), rectosigmoid (over 3 months), and lung (3 months).

Toxicity

Table 4 summarizes the frequency and type of side reactions which have been observed following intracavitary administration of Atabrine. As can be seen the two most common reactions are fever and regional pain. The temperature becomes elevated within four to eight hours after drug injection and may persist from only a few hours to as long as 10 days. The experience to date indicates that this may be due in part to the dose of Atabrine employed. With single instillations of larger doses (200 to 800 mg.) greater and more persistent fever occurs. Multiple cultures have been made of the ampules of drug and of the effusions at the height of the temperature reaction and all have been sterile. There may be, and often is, associated leucocytosis. The mechanism of the fever is presumed to be due to the chemical serositis.

The chest or abdominal pain which has been noted with considerable regularity also occurs shortly after drug administration and is considered to be an inflammatory response in the pleura or peritoneum. The severity of the pain has not usually been great and has been readily

FIGURE 6: Photomicrograph of pleura after Atabrine therapy x300. Note the marked fibrous tissue proliferation.

controlled with analgesics with or without codeine. The duration of the regional discomfort is, for the most part, shorter than the fever. In two patients with ascites, ileus developed after Atabrine instillation. The nature of the intraabdominal disease was such that this may have been a part of the natural history of the tumor.

Although no serious sequelae have been associated with the fever or pain, these are unpleasant symptoms for patients already uncomfortable from their underlying disease. In order to avoid these reactions or minimize them, the initial dose of Atabrine should be smaller than those which were employed in most of the cases briefly summarized in this study. Since Atabrine has a cumulative effect on the tumor cells it would appear probable that a larger number of small injections, with ultimate administration of the recommended total dose, will be as effective as a smaller number of injections of larger doses and that this may be accomplished without fever and pain.

Despite the total doses of 4 to 5 gm. which have been given to some patients with ascites, yellow skin pigmentation so characteristic of oral Atabrine administration has been observed only once.

More significant than any of the side reactions thus far mentioned is dyspnea which may be due to formation of adhesions between the visceral and parietal pleura or later due to contraction of the thickened, encasing pleura with concomitant reduction in lung volume. In this small series these complications have not led to major respiratory embarrassment, but the possibility suggests that bilateral neoplastic effusions should not be too quickly treated with local instillation of Atabrine on both sides. The stormy course and protracted discomfort in one patient (R. G. Case 13) who was given Atabrine in the presence of a hydropneumothorax indicates that local drug therapy should be withheld in such a circumstance until the pneumothorax has been resorbed or evacuated by closed drainage.

Studies of the peripheral blood, liver function and renal function failed to reveal any instance of systemic toxicity.

Discussion

The frequency of serous cavity effusions due to pleural or peritoneal metastases is great in the natural history of many neoplastic diseases. Although this may be the presenting finding, it is more often a late manifestation of disseminated tumor. The considerations in the management of such effusions should follow an orderly sequence. First it is important to determine which of three major mechanisms is the most important factor in the pathogenesis of the effusion since the treatment regimen will be selected from such an analysis. The differential considerations are: a) Serosal metastases; b) lymphatic obstruction centrally with distal transudation; c) cardiovascular, renal or nutritional decompensation either secondary to the neoplasm or unrelated.

The treatment of effusions secondary to cardiac. vascular, or renal functional impairment will utilize appropriate regimens of salt restriction, diuretics, cardiotonic drugs, transfusions and so on. Nutritional disturbances leading to marked reduction in serum protein and oncotic pressure will also be managed by conventional routines which are usually relatively ineffective in the presence of neoplastic disease. A careful study of a patient with neoplastic disease and an effusion will readily distinguish the mechanisms here discussed and those more directly related to the tumor.

TABLE 4 — ATABRINE TOXICITY

Total No. of Patients	No Reaction	Fever	Local Pain	Lung Compression	Ileus	Skin Pigmentation
31	11	15	12	2	2	1

It is particularly important in planning the control of neoplastic effusions to determine whether they are due to serosal metastases or to lymphatic or venous obstruction. Mediastinal tumor infiltrates with obstruction of lymph flow from the lungs or lymphangitic distribution of metastases in the pulmonary parenchyma can lead to pleural effusion. Particularly in the case of mediastinal involvement, regional radiotherapy is the therapeutic procedure of choice. Ascites unrelated to peritoneal metastases can be produced by direct extension of tumor into the central retroperitoneal area leading to a chylous effusion. Occasionally an exudate is formed from large subcapsular hepatic metastases. In these instances radiotherapy may be more useful than other measures.

When it has been demonstrated cytologically or roentgenographically that the serous surfaces are directly involved, first consideration should be given to those available forms of treatment which may modify the natural history of the disease. When, however, the tumor is refractory to more definitive measures and the effusion has been found to be recurrent, local therapy then becomes appropriate.

At the present time the local control of neoplastic effusions may be accomplished by radioactive colloidal gold or other radioactive isotopes such as yttrium and chromium or with alkylating agents such as nitrogen mustard or triethylenethiophosphoramide (thioTEPA). In reported series these procedures control effusions in about 50 per cent of the patients treated.[3,4,5] There are advantages and disadvantages of the radioactive isotopes when compared with chemotherapeutic agents. Among the former may be mentioned the infrequency of significant systemic toxicity. The disadvantages of radioactive gold include the cost of therapy and the precautions necessary to prevent radiation hazards to the individual administering the dose as well as the need to protect adjacent patients from the radiation. The alkylating drugs require no special techniques for administration and are less expensive than radioactive gold but the systemic toxicity with bone marrow depression is a constant hazard. Atabrine combines the advantages of low cost, ready availability, and absence of systemic toxicity with demonstrated effectiveness in the control of effusions caused by various types of tumors.

SUMMARY

In this preliminary report evidence has been presented which demonstrates that Atabrine (quinacrine) is effective in controlling neoplastic effusions. The number of cases available thus far for evaluation is too small to permit an accurate statement of the frequency of success. It would appear likely, however, that since the drug has a definite cytotoxic effect on tumor cells and also produces a serbsitis, it will control effusions with reasonable regularity.

The side reactions of fever, local discomfort and, rarely, yellow pigmentation (1 case) are not real hazards and probably will be reduced in frequency with the modified dosage regimen suggested in this paper. The potentially more serious compromise of lung volume by contraction of the fibrous tissue in the pleura must be weighed in patients with reduced ventilatory capacity. The ready availability of Atabrine, its low cost, apparent effectiveness against a variety of tumor types, and absence of significant systemic toxicity commend the drug for trial in the management of neoplastic effusions. It is to be reemphasized, however, that this treatment, at best, offers relief of a symptom and will not fundamentally modify the natural history of the underlying neoplastic disease.

RESUMEN

En esta comunicación preliminar se ha presentado la evidencia de que la Atebrina (Quinacrina) es efectiva para controlar los derrames neoplásicos.

El número de casos reunidos hasta ahora es demasiado pequeño para permitir una exacta estimación sobre el porcentaje de éxito.

Parecería sin embargo que, puesto que la droga tiene un efecto citotóxico definido sobre las celulas tumorales y también produce una serositis, controlaría los derrames con regularidad razonable.

Los efectos colaterales como fiebre, molestias locales y pigmentación cutánea amarilla rara vez (1 caso), no son riesgos y probablemente su frecuencia se reduzca con la modificación de la dosis que se surgirió al principio de este trabajo. La reducción potencial del volumen pulmonar por la contracción fibrosa de la pleura debe considerarse en enfermos con capacidad ventilatoria reducida.

La facilidad de obtener la Atebrina, su pequeño costo, la aparente efectividad contra una variedad de tumores y la ausencia de toxicidad general importante hacen esta droga recomendable para el tratamiento de los derrames tumorales. Se debe recalcar sin embargo que este tratamiento cuando mas ofrece alivio de un síntona y fundamentalmente no modificará la evolución de la neoplasia subyacente.

RESUMÉ

On a démontré dans ce rapport préliminaire que l'Atabrine (Quinacrine) est efficace dans la guérison des épanchements néoplasiques. On ne peut pas évaluer les resultats d'une façon definitive puisque on n'a pas eu assez des cas en traitement, mais il semble vraisemblable, cependant, que, puisque l'Atabrine exerce un éffet cyto-

toxique prècis sur les cellules tumorales et en même temps produit aussi une inflammation des séreuses il peut controler les épanchements avec une regularité appréciable.

Les réactions secondaires, comme la fièvre, discomfort local, parfois pigmentation jaune (1 cas) ne prèsent pas des dangers réels et seront probablement diminués dans leur frequence par la modification du dosage evoquée plus haut dans cette communication. L'action unfavorable sur le volume pulmonaire par contraction du tissu fibreux dans la plèvre doit être pris en considération chez les malades atteints de capacité ventilatoire réduite. La disponibilité de l'Atabrine, son prix peut élevé, son efficacité apparente contre une variété des types tumoraux, et l'absence de toxicité organique nette suggerent l'emploi du produit pour essai dans le traitement des épanchements néoplasiques. On doit cependant insister de nouveau sur le fait que ce traitement offre, au mieux, un soulagement de symptôme et ne modifie pas fondamentalement la nature de l'affection néoplasique sousjacente.

ZUSAMMENFASSUNG

In diesem vorläufigen Bericht wird gezeigt, dass Atabrin (Quinacrin) die Behandlung von Ergüssen bei Neoplasmen ermöglicht. Die Zahl der bisher auswertbaren Fälle ist noch zu gering, um die Häufigkeit von Erfolgen genau festzustellen. Dieses Medikament, das eine ausgesprochene cytotoxische Wirkung auf Tumorzellen ausübt und auch zu einer Serositis führt, dürfte aber doch ziemlich regelmässig diese Ergüsse beeinflussen.

Die Nebenwirkungen wie Fieber, lokaler Schmerz und manchmal gelbe Pigmentierung (1 Fall) sind unerheblich und können wahrscheinlich durch die oben vorgeschlagene Modifikation der Dosierung noch eingeschränkt werden.

Die möglicherweise schwererwiegende Beeinträchtigung des Lungenvolumens durch Kontraktion der fibrösen Gewebe in der Pleura muss natürlich vor allem bei Kranken mit herabgesetzter Atemkapazität in Betracht gezogen werden. Die weite Verbreitung und Billigkeit von Atabrin, die augenfällige Wirksamkeit bei verschiedenen Tumorarten, und das Fehlen von wesentlicher allgemeiner Toxizität sprechen für den weiteren Gebrauch dieses Mittels bei der Behandlung von neoplastischen Ergüssen. Es soll jedoch nochmals betont werden, dass man damit bestenfalls ein Symptom beheben kann und dass der zu erwartende Verlauf der zugrundeliegenden Geschwulsterkrankung damit nicht verändert wird.

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STAPHYLOCOCCAL ANTIBODIES IN CYSTIC FIBROSIS OF THE PANCREAS

Patients with cystic fibrosis show a relative abundance of precipitating antibodies to extracellular antigens of staphylococcus aureus. This finding strongly indicates that the staphylococci associated with the pulmonary lesions of this disease are truly involved in their pathogenesis. The observations also demonstrate that the antibody-producing mechanisms of patients with cystic fibrosis appear to be essentially intact.

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Spontaneous Perforation of the Esophagus*

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Spontaneous perforation (rupture) of the esophagus is a dire medical catastrophe in which prompt diagnosis and treatment are imperative. When the condition is untreated, the mortality rate is 25 per cent at the end of 12 hours, and it reaches approximately 70 per cent in 24 hours.[1] Survival without surgical treatment never has been recorded.[2]

Although this lesion has been recognized for more than 200 years, successful treatment dates back less than 15 years, and most cases in the literature (approximately 200 in number) have been reported in the last decade. It is doubtful that any true increase has occurred in the frequency of spontaneous esophageal perforation. It appears likely that the increasing attention given to the medical and surgical treatment of esophageal lesions has resulted in wider recognition of this unusual complication.

Esophageal perforation has rather characteristic clinical features that permit early diagnosis in most instances, yet it is apparent from review of the reported cases that this ideal frequently is not attained. The purpose of this paper is to re-emphasize the clinical features of spontaneous esophageal perforation as exemplified by our experience.

Report of Cases

Case 1: A 38-year-old man first came to the Mayo Clinic in 1946 because of vague digestive symptoms related to an excessive alcoholic intake. Roentgenographic studies of the esophagus, stomach and duodenum revealed no abnormalities. In May, 1947, after drinking heavily for 48 hours, he awakened from a drunken sleep and drank 2 quarts of cold milk, which caused some epigastric distress. An hour later, he drank a large glass of milk; he then felt nauseated and began to retch violently but was unable to empty his stomach. Excruciating pain immediately developed in the epigastrium and lower substernal region, with extension through to the back. An injection of morphine failed to relieve the pain.

The skin was cold and clammy, the pulse rate was 126 beats per minute, and the blood pressure in millimeters of mercury was 140 systolic and 80 diastolic. Physical signs of left hydropneumothorax were elicited, and this was confirmed by a thoracic roentgenogram (fig. 1). A diagnosis of spontaneous rupture of the esophagus was made, and the patient was taken to the operating room approximately 3 hours after the onset of his pain.

Left thoracotomy was performed. The left pleural cavity contained 2 liters of curdled milk, gastric juice and bile; the pleural surfaces were intensely inflamed, and the left lung was collapsed. A vertical rupture of the esophagus about 4 cm. in length was found just above the diaphragm. The perforation was closed with three rows of catgut, the pleura was closed over the esophagus, the left phrenic nerve was crushed, and closed drainage of the left pleural cavity was instituted with two catheters, a third being inserted into the mediastinum itself through the left seventh interspace.

The postoperative course was stormy, with persistent fever and toxicity, but no localized suppurative process developed. He was dismissed from the hospital on the twenty-fifth day. An esophagram a month later showed little deformity of the lower part of the esophagus, and he did not have dysphagia. He since has led a temperate life.

Comment: This case demonstrates the typical features of postemetic rupture of the esophagus; it represents one of the first reported instances of successful treatment of this lesion[3]. Despite the prompt surgical intervention, his condition was critical for the first 48 hours after operation, a circumstance probably related to his debilitated alcoholic state.

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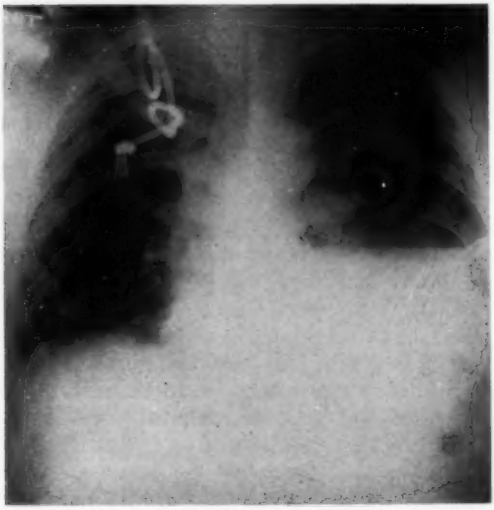

FIGURE 1 (case 1): Thoracic roentgenogram, showing left hydropneumothorax secondary to esophageal perforation. (Reproduced with the kind permission of the publishers of *Postgraduate Medicine* from Olsen and Clagett.)[3]

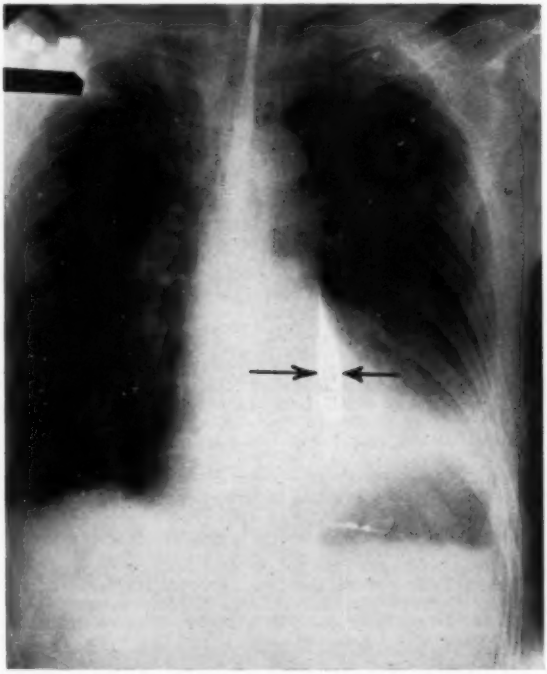

FIGURE 2 (case 2): Thoracic roentgenogram after a swallow of Lipiodol, showing passage of radiopaque medium into mediastinum (indicated by arrows). Note mediastinal widening and emphysema, with left pleural effusion.

Case 2: A 73-year-old retired physician was admitted to the hospital in August, 1955, with symptoms and signs of acute perforation of a peptic ulcer. He had had symptoms of a duodenal ulcer for 50 years, which had been well controlled previously on the usual medical regimen. Laparotomy disclosed a large perforation of the anterior wall of the duodenum. This was repaired by means of an omental patch. Atrial fibrillation developed on the following day, but this was well controlled with digitalis. Considerable gastric retention was present in the postoperative period, necessitating gastric aspiration on several occasions, but evidence of obstruction subsided without further operative intervention.

He felt well after dismissal from the hospital except for recurrent nocturnal epigastric pain relieved by antacids. A month after dismissal, acute nausea developed and he vomited once. This was followed by a moderately severe, persistent, high epigastric pain. Two hours later, he retched violently and again vomited. The pain became much worse, extending through to the back and up into the left side of the thorax to the shoulder. After several hours, he again was admitted to the hospital, where examination demonstrated boardlike rigidity of the abdominal musculature, with some suppression of intestinal sounds. A diagnosis of perforated peptic ulcer was entertained initially, but it was noticed later that subcutaneous emphysema was developing in the neck. A thoracic roentgenogram revealed mediastinal widening, mediastinal emphysema and a small pleural effusion on the left (Fig. 2). To confirm the impression of esophageal rupture, the patient was given a small amount of iodized oil (lipiodol), which was seen to extravasate from the esophagus into the lower part of the mediastinum (fig. 2).

Exploration through a left thoracotomy incision was performed approximately 18 hours after the perforation had occurred. A moderate amount of muddy gastric fluid was present in the left pleural cavity. The mediastinal pleura was disintegrated and necrotic over a large area. A vertical laceration 4 cm. in length was present on the posterolateral wall of the esophagus, extending distally to involve the gastric mucosa (Fig. 3). The perforation was closed with 000 chronic catgut in the mucosa and 000 silk in the muscular layers. The mediastinal pleura was left open; after thorough irrigation, closed drainage of the left pleural cavity was instituted. A tube was passed into the stomach to ensure continuous gastric decompression. The immediate postoperative course was uneventful. Because of continuing evidence of the obstructing duodenal ulcer, subtotal gastric resection was performed 2 months later. The patient has been well since that time.

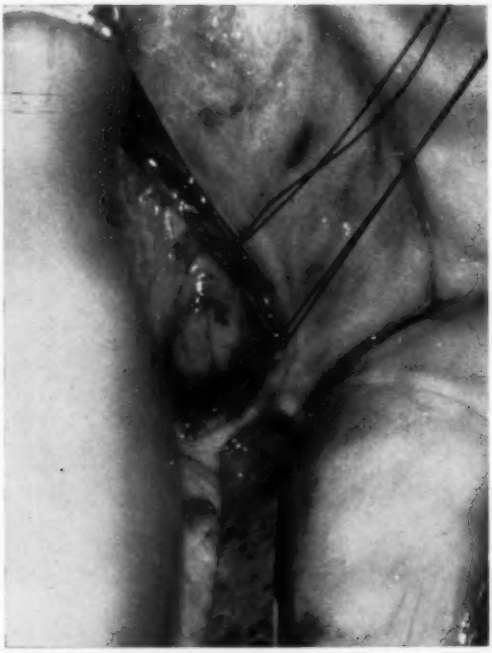

FIGURE 3 (case 2): View into left pleural cavity during operation, demonstrating the esophageal perforation.

Comment: In this case, the presence of partial obstruction at the pylorus caused the vomiting that precipitated the esophageal rupture. The previous acute duodenal perforation and the presence of abdominal rigidity were thought to indicate that the peptic ulcer had perforated again, and the correct diagnosis was not suspected until cervical subcutaneous emphysema appeared. Despite the delay in diagnosis and the advanced age of the patient, he tolerated the operation well and had an uneventful convalescence.

Case 3: A 60-year-old woman was referred to the clinic in February, 1955, for investigation of intractable edema of the legs present for 3 months prior to admission. In the preceding 18 months, she had experienced three attacks, each lasting a week, characterized by nausea, vomiting, epigastric pain and diarrhea. She was obese and had a florid complexion. Mild hypertension and diabetes mellitus were present. Measurement of the urinary excretion of 17-ketosteroids and corticosteroids and of the plasma levels of 17-hydroxysteroids confirmed the diagnosis of Cushing's syndrome.

Bilateral subtotal adrenalectomy was done through the usual lumbar incisions. Because some vomiting and a decrease in blood pressure occurred in the immediate postoperative period, a gastric tube was inserted and hydrocortisone was administered intravenously. The blood pressure became stabilized on the second day, but the patient continued to vomit despite the functioning gastric tube. On the evening of the third day, the patient began to complain of epigastric and substernal pain, which became more severe in subsequent hours. Rales were audible at the bases of both lungs, but subcutaneous emphysema was not detected. A roentgenogram of the thorax revealed no abnormalities. A diagnosis of postemetic esophagitis was made, but administration of antacids failed to relieve the pain. On the fifth postoperative day, the pain became much more severe and extended into the left side of the thorax and the left shoulder. Tachycardia and hypotension developed rapidly, and physical signs of fluid in the left side of the thorax were elicited. Thoracentesis accomplished the removal of a large quantity of fluid from the left pleural space. A diagnosis of ruptured esophagus was made, but the patient died during preparations for emergency thoracotomy.

Necropsy disclosed extensive ulcerative esophagitis, with a 1.5-cm. linear vertical laceration in the posterior wall of the esophagus beginning 2 cm. above the diaphragm (fig. 4). The left mediastinal pleura was necrotic, and a large serosanguineous effusion was present in the left pleural cavity. Moderately severe coronary atherosclerosis was noted. Acute ulceration of the duodenum was present. A carcinoma of the tail of the pancreas was found, with invasion of the splenic vein and small metastatic lesions in the liver.

Comment: Seybold and associates,[4] in reviewing 50 cases of esophageal perforation in which treatment was given at the clinic, suggested that the perforation in some instances may be limited at first to one layer of the esophageal wall. This superficial tear then leads to a localized suppurative process that subsequently breaks through the remaining layers of the esophageal wall, giving rise to mediastinitis and pleural complications. A similar mechanism might have occurred in this case. The

FIGURE 4 (case 3): Extensive esophagitis, with linear esophageal perforation at its distal end. Note the duodenal ulceration.

postoperative vomiting caused esophagitis, and a localized perforation apparently took place on the third day at the time of onset of the thoracic pain. Complete perforation presumably developed 2 days later, with more obvious mediastinal and pleural involvement and rapid death of the patient. Hypercortisonism secondary to Cushing's syndrome and postoperative steroid therapy may have been a predisposing factor. Postemetic mucosal tears at the gastroesophageal junction giving rise to massive gastrointestinal bleeding were described by Mallory and Weiss,[5] in 1929, and subsequently by others. This occurs mainly in alcoholics. It appears to be less common than is spontaneous perforation of the entire esophageal wall.

Etiology and Pathogenesis

The precipitating factor in most cases is a pronounced and sudden increase in the intraluminal pressure in the esophagus, leading to rupture of the viscus at its weakest point. In most instances, violent retching and vomiting are the immediate cause of the increased pressure, but ruptures during defecation, strenuous exercise and epileptic seizures have been reported.[2] Many authors think that, as the rupture is not truly spontaneous in origin, the term "postemetic rupture" should be used.[6]

Less commonly, the perforation apparently is secondary to peptic esophagitis.[7] In many cases in which emesis is the precipitating factor, it is likely that pre-existing esophagitis is a predisposing factor. It should be remembered that reflux esophagitis is extremely common, whereas spontaneous esophageal perforation is extremely rare. In a few instances, spontaneous esophageal rupture has occurred in a normal organ without any obvious cause.[2]

The rupture, which is always linear and longitudinal, almost invariably is situated in the lower third of the thoracic portion of the esophagus, and most frequently it involves the left posterolateral wall. This apparently is related to anatomic weaknesses in the intrinsic muscles of the esophagus in this region.[8,9] Advanced age, malnutrition and alcoholism are probably important predisposing factors.

Clinical Features

Spontaneous rupture of the esophagus is most commonly seen in men in the sixth decade of life. A previous history of alcoholism, dietary indiscretion, malnutrition or gastrointestinal symptoms is frequently obtainable.

The occurrence of the perforation is marked by the onset of excruciating pain that is poorly relieved by narcotics. The pain is usually substernal, but it may be epigastric or even lower, with associated splinting of the abdominal muscles. The pain is accentuated by deep breathing or swallowing, and aggravation is particularly evident if a patient attempts to assume a sitting position. After a variable interval, the discomfort frequently extends laterally, usually into the left side of the thorax and the tip of the left shoulder, assuming definite pleuritic characteristics.

Results of the physical examination are often diagnostic. The patient is obviously in severe pain and usually appears critically ill. Dyspnea is prominent, and cyanosis is frequently seen. Although the blood pressure may remain normal for several hours, hypotension often ensues. Physical signs of pleural fluid or hydropneumothorax frequently are elicited, but examination of the thorax may give entirely normal findings in the

early stages of the disease. The precordial "crunch" of mediastinal emphysema may be noted. The appearance of subcutaneous emphysema in the cervical region is an extremely important diagnostic feature, but this may be delayed for several hours. Rigidity of the abdominal musculature is relatively common and may lead to an erroneous diagnosis of a perforated intra-abdominal viscus.

Diagnosis

The diagnosis of spontaneous esophageal rupture usually can be made from the history and physical examination alone. Results of roentgenographic studies are conclusive when the diagnosis is doubtful. Errors in diagnosis usually are caused by unawareness of the symptoms of esophageal rupture or failure to consider the possibility that this lesion is present.[2] Barrett[10] noted the diagnostic triad of rapid respiration, abdominal rigidity and subcutaneous emphysema, but Mackler's[9] triad of vomiting, low thoracic pain and emphysema of the neck is equally helpful in suggesting the possibility of esophageal perforation.

The frequent presence of epigastric pain and abdominal rigidity may direct attention toward the diagnosis of an intra-abdominal lesion, but the physical and roentgenographic signs of intrathoracic disease almost always clarify the picture.

A thoracic roentgenogram always should be obtained, preferably with the patient in the upright position. Mediastinal emphysema is usually, and perhaps always, present after perforation of the thoracic portion of the esophagus;[1] this may be detectable roentgenologically before any physical signs have appeared. Naclerio[11] has described a "V" sign due to linear air shadows corresponding to the fascial planes of the mediastinal and diaphragmatic pleurae near the lower part of the esophagus. Mediastinal widening, subcutaneous emphysema in the cervical region, pleural effusion and hydropneumothorax usually are seen in the thoracic roentgenogram, particularly if some time has elapsed since the onset of symptoms. In some cases, mediastinal pleural rupture occurs immediately, and hydropneumothorax develops early. Aspiration of the pleural space yields gastric contents. If the diagnosis is in doubt, a swallow of roentgenographic opaque medium usually will extravasate in to the mediastinum or pleural cavity and can be demonstrated on the plain roentgenogram.

Rupture of the supradiaphragmatic portion of the stomach in an esophageal hiatal hernia may closely simulate perforation of the esophagus. Although careful roentgenographic studies may permit differentiation of these two conditions, the distinction is of no practical importance, as both lesions should be treated by immediate operation.

Treatment

Early diagnosis and prompt surgical intervention are the cornerstone of treatment in spontaneous esophageal perforation. Supportive therapy in the form of narcotics, oxygen, antibiotics, intravenously administered fluids and transfusions will improve the patient's general condition, but each passing hour lessens the chance of survival. The presence of hypotension should not delay operation, since this usually improves with

evacuation of the irritating gastric secretions from the pleural cavity, closure of the rent in the esophagus, and re-expansion of the lung. No instance of survival with strictly medical management has been reported.

Simple drainage of the mediastinum and pleural cavity may be life-saving, and in such a situation one is willing to accept the increased morbidity. If the patient is seen late following esophageal perforation, his condition may only permit such drainage procedures. The surgical treatment of choice is primary closure of the perforation via a transpleural approach.[12] The mucosa is accurately closed with fine chromic catgut, and the layers of muscle are approximated with fine silk sutures. The mediastinal pleura is left open, and the pleural space is drained by means of an intercostal catheter attached to suction. A transnasal tube is passed into the stomach at the time of the operation for gastric decompression.

Transthoracic closure of the esophageal perforation has resulted in survival in 75 per cent of cases in one series.[2] With early diagnosis and operation, one can expect these figures to improve.

SUMMARY

Spontaneous rupture of the esophagus is a rare catastrophe that is usually secondary to violent retching and vomiting. Esophagitis is probably a precipitating factor. The development of the lesion is characterized by the sudden onset of severe epigastric, retrosternal or thoracic pain, which is followed by dyspnea, cyanosis and shock. Examination discloses evidence of pleural effusion or hydropneumothorax in most instances. The development of subcutaneous emphysema in the neck is an important diagnostic feature. Roentgenologic findings are characteristic and usually confirm the diagnosis. The most important factor in reaching an early diagnosis is the awareness of the possibility of the lesion having occurred. Surgical intervention is most successful when done early in the course of the illness.

RESUMEN

La ruptura espontánea del esófago es un accidente raro generalmente consecutivo a eructos violentos y vómitos. La esofagitis es probablemente un factor precipitante. El desarrollo de esta ruptura se caracteriza por dolor repentino epigástrico, retroesternal o torácico, que es sequido de disnea, cianosis y schock. El examen físico revela la presencia de derrame pleural o hidroneumotórax en la mayoría de los casos. La presencia de enfisema subcutáneo en el cuello, es una característica diagnóstica importante. Los hallazgos radiológicos son característicos y habitualmente confirman el diagnóstico. El factor más importante para el diagnóstico consiste en estar alerta ante la posibilidad de esta lesión. El tratamiento quirúrgico el lo más satisfactorio cuando se hace tempranamente.

RESUMÉ

La rupture spontanée de l'oesophage est une catastrophe rare qui est habituellement secondaire à de violentes nausées et à des vomissements. L'oesophagite est probablement un facteur adjuvant. Le cours évolutif da la lésion est caractérisé par l'apparition soudaine d'une douleur épigastrique sérieuse, rétrosternale ou thoracique, suivie de dyspnée, de cyanose et de shock. L'examen révèle dans la plupart des cas l'existence d'un épanchement pleural ou d'un hydropneumothorax. Le développement d'un emphysème sous-cutané cervical est un élément de diagnostic important. Les constatations radiologiques sont caractéristiques et confirment généralement le diagnostic. Le facteur le plus important pour arrifer à un diagnostic précoce est la connaissance de la possibilité d'un tel accident. L'intervention chirurgicale a beaucoup plus de chance de réussir quand elle est effectuée à un stade précoce de l'affection.

ZUSAMMENFASSUNG

Eine Spontanruptur der Speiseröhre ist eine seltene Katastrophe und gewöhnlich die Folge heftigen Würgens und Erbrechens. Eine Speiseröhrenentzündung ist wahrscheinlich ein wegbereitender Faktor. Der Verlauf des Krankheitsbildes ist gekennzeichnend durch plötzlishes Einsetzen einer schweren epigastrischen retrosternalen oder thorakalen Schmerzempfindung, an die sich Dyspnoe, Cyanose und Schock anschliessen. Die Untersuchung ergibt in den meisten Fällen Anzeichenn eines pleuralen Ergusses oder eines Hydro-Pneumothorax. Das Auftreten eines subkutanen Emphysem am Hals ist ein wichtiges diagnostisches Merkmal.

Die röntgenologischen Befunde sind charakteristisch und bestätigen gewöhnlich die Diagnose.

Der wichtigxste Umstand, um zu einer Frühdiagnose zu kommen, ist das Gewahrwerden der Möglichkeit, dass eine solche Erkrankung vorliegen könnte. Chirurgisches Vorgehen ist am Meisten erfolgreich, wenn es frühzeitig im Krankheitsablauf erfolgt.

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CARBON DIOXIDE AND RESPIRATION IN ACID-BASE HOMEOSTASIS

The amazing primary reactivity required for acid-base and oxygen homeostasis and the coordinated stabilization of its remotely separated components, is dependent almost entirely upon the unique combination of physical and chemical characteristics of the CO_2 produced by the cells of the same regulating system. However, in responding to local changes, the respiratory neurons cause alterations in the acid-base composition of arterial blood and other fluids which modify the local environments of many other cells. Only the small fraction of these cells showing intrinsic reactivity to acid-base change are capable of responding and, hence, acute active homeostatic regulation of the internal environment is restricted to the reactive cell types. These cells, including central respiratory neurons, vascular smooth muscle cells and chemoreceptor glomus cells, exist in their most stable states at entirely different acid-base levels and provide independent sensing components in the fluctuating, dynamic interaction of factors concerned with acute adjustment of the acid-base composition by the total respiratory control mechanism.

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SECTION ON CARDIOVASCULAR DISEASES

Atrial Septal Defects of the Sinus Venosus Type: Surgical Considerations

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Developments in the field of open heart surgery have stimulated interest in many cardiac lesions which were previously considered to be of no practical importance. Only a few years ago, for example, the diagnosis of "interatrial septal defect" was considered adequate for practical purposes, whereas at present the necessity for differentiating ostium secundum from ostium primum defects is fully appreciated. Thus, in considering defects of the interatrial septum, emphasis is now being placed upon a precise and complete anatomic diagnosis. Defects in the septum secundum may be of several relatively uniform types in regard to location, size, and relation to the ostia of the venae cavae and pulmonary veins. A unique anomaly is the so-called sinus venosus defect which is a lesion located in the septum secundum portion of the interatrial septum and which has a relatively consistent anatomic relationship to the septum and great veins. Since it is a relatively common type of atrial defect, certain aspects of embryologic and clinical significance deserve consideration.

Characteristically the sinus venosus defect is located adjacent to the orifice of the superior vena cava and no superior margin of the atrial septum is present (Fig. 1). Thus, the ostium of the superior vena cava appears to override the septum and empty into both the right and left atria. The lesion is located cephalad to the fossa ovalis which is usually intact. Anomalous drainage of pulmonary veins from the right upper and sometimes middle lobe is usually part of the anatomic complex, and the point of entry of the veins is at the atriocaval junction or higher. In many instances one or more segmental pulmonary veins of the right upper lobe drain into the superior vena cava (Fig. 2).

An anatomic description of this lesion by Wagstaffe[17] appeared in 1868, and subsequently several other examples were described in post mortem specimens.[1,2,8] In 1957 Watkins and Gross[16] referred to a superior marginal defect occurring in 15 cases among 43 cases of atrial septal defect, and some of these were associated with anomalous drainage of the sinus venosus type. Lewis[11] in an excellent description of the anatomy of atrial defects encountered at operation used the term "high septal defect" for

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the type of lesion now under consideration. Bedford, et al[3] described the catheterization findings of this lesion which they called a superior caval defect. Ross[14] subsequently coined the term sinus venosus defect which seems to be suitable since it points out the embryologic origin of the lesion.

Embryology

Numerous theories regarding embryology of this lesion have been proposed, and these were recently reviewed in a comprehensive report by Harley.[7] In general, all explanations implicate an abnormality in development of the sinus venosus. This structure is present in the embryo at the three-to-four-week stage as a collecting reservoir, receiving venous blood from the common cardinal veins. It is located in the midline posteriorly and empties into the common atrium (Fig. 3A). At the fourth or fifth week the right superior cardinal vein enlarges to form ultimately the superior vena cava. The left superior cardinal vein begins to atrophy, and its remnant forms the coronary sinus and the oblique vein of Marshall. The result of these changes is a shift of the sinus venosus to the right. At this time (five weeks) the atrial septa begin to develop with the septum primum originating on the dorso-cephalic portion of the atrium (Fig. 3B). The ostium secundum develops in the septum primum as it makes contact with the endocardial cushions to close the ostium primum.

Under normal circumstances by the sixth week the sinus venosus has been incorporated into the right atrium, and the superior cava shifts to its normal position on the right (Fig. 3B). This leaves an interseptoval-

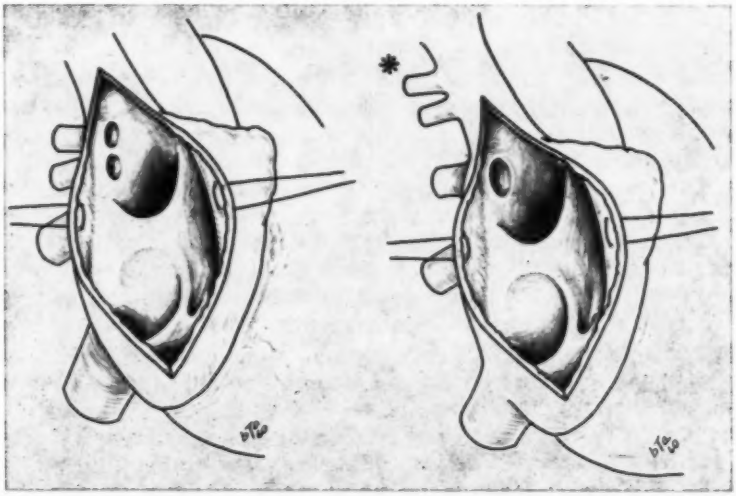

FIGURE 1 (left): Drawing showing the anatomic characteristics of a typical sinus venosus type of atrial septal defect. The defect is located high in the septum and the superior septal margin is absent. Veins from the right upper and occasionally middle lobes drain anomalously into the right atrium. FIGURE 2 (right): Drawing showing a variation of usual sinus venosus defect in which the pulmonary veins of the right upper lobe are implanted directly into the superior vena cava. This type of venous drainage requires special consideration from the standpoint of surgical repair.

vular space between the valve of the superior cava and the septum primum for the development of the septum secundum. With normal development of this structure the ostium secundum is partially covered, remaining patent only as a foramen ovale (Fig. 3C).

Lewis[11] pointed out that the atrial defect of the sinus venosus type lesion was located in the position of the ostium secundum of the septum primum. Harley[7] suggested that the crucial developmental failure was a consequence of failure of the sinus venosus to shift to the right from its midline position. As a result the superior cava enters the right atrium at a point nearer than normal to the septum primum leaving no intervalvuloseptal space for the cephalic development of the septum secundum (Fig. 3B'). Thus, the septum secundum is defective superiorly, and inferiorly it forms the annulus of the fossa ovalis. Since the ostium secundum remains uncovered superiorly (Fig. 3C'), this explains the presence of a high atrial defect.

The means by which the pulmonary veins attach to the atrio-caval junction is not so clear. Shaner[15] has pointed out the close approximation of the right pulmonary veins and superior vena cava in the developing embryo. It seems possible that with absorption of the sinus venosus into the right atrium and the formation of the superior cava, the attachment of the upper pulmonary veins might shift to the atrio-caval junction. This explanation hardly seems adequate, however, to explain the occasional entry of the right superior pulmonary vein high into the superior cava, and this phase of the developmental anatomy remains obscure.

Clinical Considerations

The incidence of this lesion among our cases of atrial septal defects of the septum secundum type undergoing open cardiac repair was approximately 10 per cent since 17 cases were encountered in a series of 164 patients. Age span ranged from nine months to 48 years, four patients being less than 10 years old, seven between 10 and 30 years, and six patients more than 30 years old. There were 13 males and 4 females.

History and physical findings were indistinguishable from those of patients having septum secundum defects. Roentgenograms revealed an increase in pulmonary vascular markings. Occasionally the diagnosis was suggested by a right hilar bulge at the atrio-caval junction, representing the anomalous pulmonary veins. Dow[4] recently described roentgenographic findings of sinus venosus defects using tomography and angiocardiography which should assist in preoperative diagnosis of the lesion.

Electrocardiographic findings were also similar to those of an atrial defect of the septum secundum type. Seven patients had a right bundle branch block and 6 showed right ventricular hypertrophy.

Cardiac catheterization usually revealed a left-to-right shunt, and in 12 patients the step-up in oxygen saturation was found to be at the atrio-caval level. In 10 cases the catheter entered a right pulmonary vein, usually directly from the superior vena cava. Two patients had a right atrial pressure above 10 mm. Hg, and 5 had a pulmonary artery pressure (systolic) above 30 mm. Hg. In one patient having severe mitral and tricuspid regurgitation as a result of rheumatic heart disease cath-

eterization failed to demonstrate a left-to-right shunt at the atrial level. Dye dilution studies as described by Swan, et al[16] were not routinely performed in these patients.

At operation all of our patients had a high atrial septal defect without a superior margin (Fig. 1 and 2). The foramen ovale was also patent in one case. Anomalous pulmonary venous drainage was present in all cases, usually the upper and middle lobe veins draining into the superior cava at its junction with the atrium. In three cases a persistent left superior cardinal vein (left superior vena cava) was demonstrated, draining into the coronary sinus. The frequency of this associated vascular anomaly has been previously described.[4] Thus, in all instances of sinus venosus type of atrial defect, the left superior mediastinum should be inspected at the time of thoracotomy for failure to detect this anomaly will lead to technical complications during the cardiopulmonary bypass.

Technical Considerations of Repair

Various technics have been described for the correction of this lesion. Lewis[11] first reported use of a partial purse string suture along the superior margin of the defect which vertically closed the defect and diverted

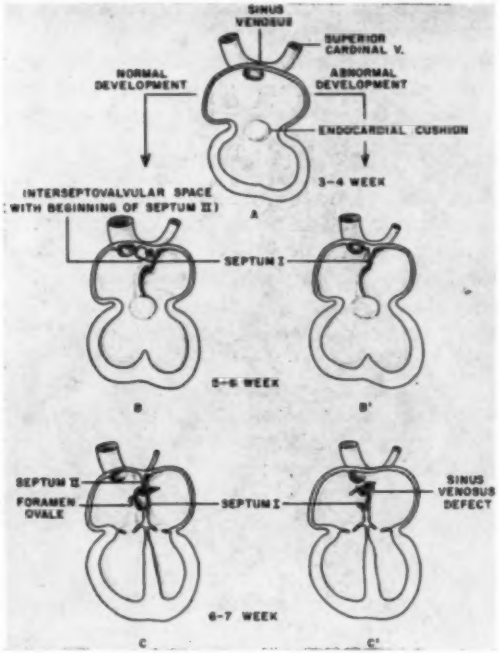

FIGURE 3: Diagrams showing normal (A,B,C) and abnormal (B',C') development of interatrial septum. Normally the sinus venosus (A) shifts toward the right as the left superior cardinal vein atrophies. The septum primum and right superior vena cava are separated by an interseptovalvular space (B). In this space the septum secundum develops and descends closing the ostium secundum which may remain only as a foramen ovale (C).

In B' the sinus venosus failed to migrate far enough toward the right so that the interseptovalvular space is absent. The septum secundum does not form superiorly and the ostium secundum remains open without a superior margin, forming a typical sinus venosus atrial septal defect (C').[7]

blood flow from the anomalous pulmonary veins into the left atrium. A similar approach involves the partitioning of the superior vena cava and superior pulmonary vein so as to divert drainage from each into its proper chamber.[9,13] These technics have the disadvantage of narrowing the point of entry of either or both the superior cava and the anomalous pulmonary veins into the heart. Subsequently Lewis[12] suggested another technic which included transection of the superior vena cava with anastomosis of the upper portion of the cava into the right atrial appendage. The lower caval segment serves as a conduit to the left atrium through the atrial defect. This somewhat complicated technic has the objectionable disadvantage that subsequent stenosis and thrombosis of the atriocaval anastomosis may occur.

Brock[4] has suggested that postoperative complications resulting from obstruction to systemic and pulmonary veins could be avoided by closing the septal defect in a direction transverse to the direction of caval flow. Using interrupted sutures, he pulled the inferior margin of the septum cephalad, attaching it to the caval wall above the anomalous venous opening. If the defect were even of moderate size, this method would produce tension on the suture line and distort either the cava or the pulmonary veins, predisposing to venous obstruction or recurrence of the defect. Kirklin[10] used an Ivalon (polyvinyl) patch to form a tunnel between the orifices of the anomalous pulmonary veins and the high atrial defect. He advocated the semi-open technic employing Gross's atrial well. We favor this basic approach in actual repair of the anomaly believing that the septal tissue available locally must be supplemented by a prosthesis to prevent tension and distortion (Fig. 4a and b). Unlike Kirklin, however, we recommend an open procedure utilizing total cardiopulmonary bypass. In our patients a knitted Dacron fabric patch

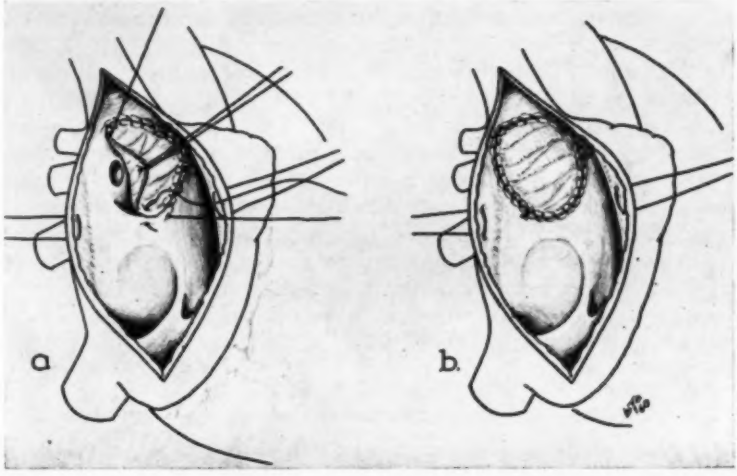

FIGURE 4: Drawings showing technic of repair of a sinus venosus type of atrial septal defect. In (a.) the knitted Dacron patch is being sutured over the interatrial communication in a position which directs the flow from the anomalous pulmonary veins into the left atrium. In (b.) the defect is repaired without tension and without constriction or distortion of pulmonary veins or superior vena cava.

was sutured over the septal defect along the inferior margin of the defect and anterior margin of the anomalous pulmonary veins in order to divert blood from the pulmonary veins into the left atrium. A continuous suture of 4-0 black silk with fine needles was used to obtain a precise and accurate repair. This technic was employed in 15 cases of this group.

In two patients a portion of the venous drainage of the upper lobe entered the superior vena cava in an unusually cephalad position (Fig. 2). In these cases the middle lobe vein was diverted into the left atrium with a purse string suture closing the atrial defect without a prosthesis. In one case the right upper lobe was resected and in the other the segmental arteries which supplied the corresponding portion of the upper lobe were ligated.

In the patient with a serious degree of mitral and tricuspid regurgitation a plastic repair of these valves was necessary. The heart was entered from a right postero-lateral incision opening the left atrium just anterior to the right pulmonary veins. Annuloplasty was performed, approaching the tricuspid valve through the septal defect and the mitral valve directly. Competence of both valves was obtained. The sinus venosus defect was repaired with a patch of Dacron knitted cloth, using the left atrial approach for this purpose.

Results

In our series of 17 patients only one death occurred after open repair of the sinus venosus defect. The patient was a 48-year-old man with severe pulmonary hypertension who was operated upon in November 1958. Right atrial and pulmonary arterial pressures were 25/5 and 70/20 mm. Hg, respectively. Hemothorax was noted 12 hours after operation, and thoracotomy was performed for evacuation of the clotted blood. Death occurred 24 hours after operation and was thought to be related to the pulmonary hypertension. Permission for autopsy was refused. The risk of operation in such patients in the older age group with pulmonary hypertension and increased right atrial pressure is now recognized, and operation is usually not recommended unless there is evidence of a left-to-right shunt indicating low pulmonary vascular resistance. Except for the hemothorax in this patient, only one other complication occurred. Nodal rhythm developed during the actual repair of the lesion in a three-year-old patient and persisted for three weeks after operation when sinus rhythm resumed. Surgical injury to the sino-atrial node may explain this complication although it was not observed in other cases. All other patients of this series made a complete and uncomplicated recovery.

Discussion

The favorable results obtained in our cases with relative freedom from complications after operation was indeed gratifying since postoperative morbidity and mortality has been reported by others. Lewis,[12] for example, reported death in a patient from superior vena cava obstruction following direct suture repair. From the same series were three patients who had respiratory difficulty from pulmonary venous obstruction following surgery. In performing cardiac catheterization following closure of a sinus venosus type defect by atrioseptopexy, Carlgren and Petterson[3] found a pressure

gradient of 8 to 10 mm. Hg between the superior vena cava and the right atrium. This finding indicated that the repair had compromised the lumen of the superior caval orifice.

In our opinion, repair of the entire sinus venosus anomaly may be accomplished with minimal risk if certain principles of surgical technic are followed. First, the defect should be corrected using temporary cardiopulmonary bypass since this method provides adequate time to perform an unhurried and accurate repair. Second, the septal defect must be closed without tension, usually employing a synthetic prosthesis over the defect. Third, the diameter of the orifice at the atrio-caval junction must not be compromised. Fourth, the drainage of pulmonary venous blood from the right upper lobe must be free and unobstructed. If the veins are located in a particularly unfavorable position for easy diversion into the left atrium, one should consider leaving their caval connection undisturbed. Since the septal defect is responsible for most of the left-to-right shunt, the volume of anomalous flow from these veins is usually not sufficient to produce a clinically significant intracardiac shunt once the atrial septal defect is repaired. One should avoid, therefore, complicated venous anastomoses or vascular grafts since the risk of technical failure with the serious consequences of lobar pulmonary infarction far exceeds the benefit the patient may derive from having a complete anatomic repair. There are several safe and acceptable methods of dealing with these veins in patients in whom it is not feasible to perform a complete repair by using an intracardiac prosthesis alone. We do not advocate right upper lobectomy in children if the upper lobe veins are large and numerous and cannot be repaired while closing the defect. If the remaining veins are small and particularly if the patient is an adult, we would probably ignore these vessels rather than attempt a repair. Ligation of the corresponding segmental arteries, although successful in one of our cases, probably does not provide an acceptable solution to this technical problem. Ligation of the segmental pulmonary veins as suggested by Brock,[4] which was successful in his two patients, is now also recommended by us.

SUMMARY

The sinus venosus type of atrial septal defect is a common lesion located in the upper portion of the septum which is characteristically associated with anomalous drainage of pulmonary veins. Hemodynamic effects resemble those of any atrial defect located in the septum secundum or upper portion of the septum. Surgical repair of the lesion should be done utilizing temporary cardiopulmonary bypass, and recognition by the surgeon of the technical problem is important. Closure of the septal defect and transposing the anomalous pulmonary veins usually necessitates use of a patch prosthesis for complete repair without producing stenosis of the veins.

RESUMEN

El defecto del tabique auricular del tipo seno venoso, es común en la parte superior del tabique que está característicamente asociado con canalización anómala de las venas pulmonares.

Los resultados hemodinámicos se asemejan a los de cualquier defecto auricular ubicados en el septum secundum o parte superior del tabique. La corrección quirúrgica de ese defecto debe hacerse usando la desviación circulatoria temporal y es importante que el cirujano conozca bien el problema.

El cierre de la falla septal y la transposición de las venas pulmonares anómalas requiere el uso generalmente de protesis de parche para la reparación completa sin producir la estenosis de las venas.

RESUMÉ

Dans le cas de persistance de communication interauriculaire la forme à type de sinus veineux est une lésion banale. Localisée dans la portion supérieure de la paroi, elle est associée d'une façon caractéristique à un drainage anormal des veines pulmonaires. Les effets hémodynamiques ressemblent à ceux de toute communication auriculaire localisée au septum secundum ou dans la portion supérieure de la cloison. La réparation chirurgicale de la lésion devrait être faite en utilisant la circulation extracorporelle temporaire, et l'évaluation par le chirurgien du problème technique est importante. La fermeture de l'altération auriculaire et la transposition des veines pulmonaires anormales nécessite généralement l'emploi d'une plaque de prothèse pour obtenir une réparation complète sans créer une sténose des veines.

ZUSAMMENFASSUNG

Der Atrium-Septum-Defekt von Sinus-venosus-Typ stellt eine häufige, in den oberen Abschnitten des Septums lokalisierte Läsion dar, die charakteristisch mit anormaler Einmündung der Pulmonalvenen verbunden ist. Die hämodynamische Wirkung gleicht der jedes Atriumdefektes, der im Septum secundum oder im oberen Teil des Septums gelegen ist. Der chirurgische Defektverschluß sollte unter zeitlicher Umgehung des Herzlungenkreislaufes durchgeführt werden, wobei die Beachtung des technischen Problems durch den Chirurgen wichtig ist. Vollständiger Verschluß des Septumdefektes und Verlegung der anormal mündenden Pulmonalvenen zwigen gewöhnlich zur Verwendung einer Prothese, die ein Stenosieren der Venen verhindert.

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CARDIAC INSUFFICIENCY IN CHRONIC ALCOHOLISM

The frequent coexistence of malnutrition and heart disease with an obscure cause is a worldwide phenomenon. In only a few instances has a causal relationship between these entities been accepted, e.g., kwashiorkor, beriberi. Nevertheless, circumstances suggest similar instances which demand further study.

Consideration must also be given to the possibility that alcohol *per se* may have a direct toxic effect on the heart.

In eight cases reviewed, the clinical picture and course ranged from that of classic beriberi heart disease to typical nonspecific heart failure. In every instance, alcoholism was a prominent feature of the clinical syndrome.

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Bronchial Blood Flow in Patients with Chronic Pulmonary Disease and Its Influences Upon Respiration and Circulation*

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Anatomically and histologically, it has been pointed out by several investigators[1-7] that enlargement of the bronchial arteries and development of the pulmonary collateral circulation are common features associated with various chronic pulmonary diseases and some cardiac anomalies. However, the bronchial vascular system, owing to its structural peculiarity, is quite difficult to investigate physiologically in human subjects, so that the measurement of the volume rate of flow through such vessels has been almost restricted to animal preparations except for a few attempts.

The measurement of pulmonary collateral blood flow in man was first attempted by Bing, Vandam and Gray[8,9] in 1947, in congenital heart disease with the stenosed pulmonary artery. This method was later applied in this laboratory to the measurement of bronchial blood flow in several pulmonary diseases,[10] but the method seemed to be unsuitable because of the complexity of the experimental procedures and of unexpected experimental errors. Recently, Fishman, Turino, Brandfonbrener and Himmelstein[11] reported the measurement of "effective" pulmonary collateral blood flow in man by means of a combined technique with the bronchospirometry and the unilateral occlusion of the pulmonary artery. However, this method also appears considerably troublesome and complicated in its performance.

In order to measure simply and accurately the total bronchial blood flow in man, a method has been proposed in the preceding report.[12] The purpose of the present paper is to report the results of measurement of bronchial blood flow in patients with a variety of chronic pulmonary disease by this method, and to describe the influences of the bronchial blood flow upon respiration and circulation on the basis of such results.

Materials and Methods

For this investigation, 50 patients with various chronic pulmonary diseases were studied. Of this number, eight had bronchiectasis, eight pulmonary tuberculosis, 14 silicosis or silicotuberculosis, four pulmonary abscess, eight pulmonary emphysema, and eight pulmonary neoplasms. Some clinical data of these patients are outlined in Table 1.

All of the patients were studied in the supine position in the postabsorptive state without sedatives. Under fluoroscopic guidance, two cardiac catheters were introduced into the antecubital veins and advanced until the respective tips lay in the main pulmonary artery and

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in the superior vena cava. A Cournand needle was inserted into the brachial artery. The measurements of the left and right ventricular outputs were performed by the method previously reported.[13] Immediately before and after this procedure, expiratory gas was collected in a Douglas bag through a mouth piece for five minutes, and simultaneously arterial blood and mixed venous blood were sampled. The gas was analyzed for oxygen and carbon dioxide by the Scholander micrometer apparatus and oxygen consumption and RQ were calculated. The blood samples were analyzed for total oxygen content, oxygen capacity and carbon dioxide content by the manometric technique of Van Slyke and Neill, and for oxygen tension and carbon dioxide tension by the direct method of Riley. Venous admixture ratio was calculated by means of high and low oxygen breathing according to Riley, Cournand and Donald. Pulmonary artery pressure was measured by the Sanborn capacitance electromanometer.

For measurements of heart size on teleroentgenogram, four indexes, i.e. transverse diameter, cardiothoracic ratio, frontal area, and the ratio indicated by the product of the long and broad diameter of heart divided by the product of the height and width of thorax ($\frac{L \times B}{H \times W}$), were employed and abnormal values were determined according to Stroud.[15] The predicted values for the transverse diameter and the frontal area were obtained using the nomogram of Stroud from height and weight. The heart was considered to be enlarged if the transverse diameter and the frontal area are over 15 per cent and 10 per cent in excess of the

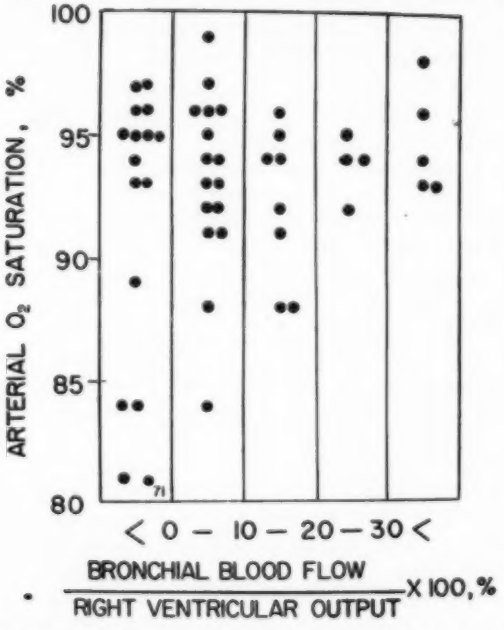

FIGURE 1: Relation between bronchial blood flow and arterial O_2 saturation in patients with various pulmonary diseases.

predicted value respectively. For the cardiothoracic ratio and the $\frac{L \times B}{H \times W}$ the heart was considered to be enlarged if the ratios exceed 50 per cent and 28 per cent respectively.

Results

Bronchial blood flow, arterial oxygen saturation, venous admixture ratio and pulmonary artery pressure are shown in Table 2. Systemic pressure and the four indices of the cardiac silhouette on teleroentgenogram are shown in Table 3.

Bronchial Blood Flow

Bronchiectasis — The left ventricular output was found to be greater than the right in all eight cases with bronchiectasis studied. The bronchial blood flow was quite variable. Two of the subjects (H. S. and K. S.) showed definitely increased bronchial flow. Two other subjects (A. T. and K.I.) showed equivocal high values for bronchial blood flow, the left ventricular output exceeding the right ventricular output by 11 per cent. The remaining four showed flows within the normal range. The large bronchial blood flow in subject K.S. was unexpected and will be discussed later. The increase in bronchial blood flow appeared to be related to the extent of the affected lung and was more marked in cystic bronchiectasis than in cylindrical.

Pulmonary tuberculosis — Bronchial blood flows of 1.34 l./min. and 2.59 l./min. were measured in two of eight cases with pulmonary tuberculosis, but in the other cases no increase in bronchial blood flow was obtained. These two cases with the increase in bronchial blood flow showed productive shadows on chest roentgenogram and one of them (A.A.) had undergone pulmonary resection of the left upper lobe and supplementary thoracoplasty five years before the study. Three of six cases without increase in bronchial blood flow had many cavities and two had extensive tuberculous bronchiectasis. The latter stands in sharp contrast to nontuberculous bronchiectasis described above. There was no relation between the extent of lesions and the increase in bronchial blood flow.

Silicosis — A significant increase in bronchial blood flow was measured in 3 of 14 silicotic patients, the highest value being 2.78 lit/min, 55.6 per cent of the right ventricular output. Two subjects (S.Y. and C.Y.) showed an equivocal increase in blood flow. The increased bronchial blood flow was not observed in the cases with the first grade or the second grade silicosis without tuberculous complication, while significantly increased flow was frequently observed in silicosis with massive densities on chest roentgenograms.

Pulmonary abscess — In all four cases with pulmonary abscess the left ventricular output exceeded the right, but the difference between the two outputs, which implies bronchial blood flow, was so small, ranging from 0.9 to 8.0 per cent of the right ventricular output, that certainly appears to be of no significance. In three of the four cases active inflammation had subsided on chemotherapy at the time of study, while the other one (K.W.) had active inflammatory lesions in the right upper

TABLE 1—CLINICAL DATA OF 50 PATIENTS STUDIED

Subject	Sex	Age	Body Surface Area (m^2)	Classification and Complications
			Bronchiectasis	
C.S.	M	49	1.62	Cylindrical, 1 Segment
M.T.	F	16	1.52	Cylindrical, 2 Segments
S.A.	M	22	1.52	Cylindrical, 2 Segments
A.T.	M	26	1.50	Cylindrical or Cystic, 2 Segments
K.I.	M	34	1.30	Cystic, 4 Segments
T.K.	M	33	1.42	Cystic, 5 Segments
H.S.	M	29	1.52	Cystic, 10 Segments
K.S.	M	26	1.50	Cystic, 10 Segments
			Pulmonary Tuberculosis	
T.I.	M	23	1.55	Moderately, Tuberculous Bronchoiectasis
M.H.	M	33	1.86	Moderately
K.S.	M	33	1.54	Moderately, Productive
A.A.	M	30	1.59	Moderately, Left Upper Lobe Resection and Supplementary Thoracoplaty 5 Years Ago
S.O.	M	40	1.59	Moderately, Cavities
R.Y.	F	26	1.55	Far Advanced, Destroyed Lung, Tuberculous Bronchiectasis
R.K.	M	33	1.63	Far Advanced, Cavities
K.M.	F	50	1.43	Far Advanced, Productive, Cavities
			Silicosis	
T.Y.	M	45	1.72	I Grade, T-B Minimal
J.O.	M	40	1.32	I Grade, T-B Minimal
To.K.	M	48	1.44	I Grade, T-B Minimal
M.Y.	M	57	1.43	I Grade, T-B Minimal
T.T.	M	54	1.42	I Grade, T-B Moderately
M.T.	M	55	1.44	II Grade
T.I.	M	56	1.61	II Grade
S.H.	M	66	1.42	II Grade, T-B Minimal
C.F.	M	57	1.24	III Grade, T-B Minimal
S.Y.	M	46	1.61	III Grade, T-B Advanced, Cavities
Ta.K.	M	35	1.44	III Grade, T-B Minimal
T.O.	M	55	1.39	Massive Density
C.Y.	M	51	1.51	Massive Density
M.K.	M	63	1.62	Massive Density
			Pulmonary Abscess	
H.S.	M	34	1.70	Almost Recovered, Residual Cavity in Left Lower Lobe
M.Y.	M	24	1.52	Almost Recovered
B.O.	M	21	1.46	Almost Recovered
K.W.	M	32	1.52	Active Inflammatory Lesion in Upper and Middle Lobes
			Pulmonary Emphysema	
K.U.	M	59	1.43	Bronchial Asthma
T.Kr.	M	70	1.36	Chronic Bronchitis
S.Y.	M	47	1.48	Bronchial Asthma
S.Sm.	M	49	1.25	Bronchial Asthma
H.K.	M	57	1.45	Bronchial Asthma
S.Sa.	M	61	1.61	Bronchial Asthma
J.S.	M	54	1.42	Bronchial Asthma
T.Ka.	M	53	1.48	Chronic Bronchitis
			Pulmonary Neoplasms	
K.S.	M	67	1.64	Bronchogenic Carcinoma in Right Upper Lobe
Y.S.	M	52	1.54	Bronchogenic Carcinoma in Right Upper Lobe
D.I.	M	53	1.33	Bronchogenic Carcinoma, Atelectasis in Right Lung
F.S.	F	32	1.29	Bronchogenic Carcinoma, Complete Atelectasis in Right Lung
K.Su.	M	59	1.45	Bronchogenic Carcinoma, Carcinomatous Pleurisy
K.Si.	F	28	1.34	Metastatic Carcinoma from Thyroid Gland
K.W.	M	47	1.51	Metastatic Carcinoma from Thyroid Gland
C.T.	M	48	1.64	Metastatic Carcinoma from Thyroid Gland, Pneumonia in right middle and lower lobes

and middle lobes at the time of study and complained of severe cough and profuse sputum.

Pulmonary emphysema — Of eight cases with pulmonary emphysema, seven did not show an increase in bronchial blood flow, while the remaining one (T. Ka.) showed the bronchial blood flow a little more than 10 per cent of the right ventricular output. The etiology of emphysema in six of the seven cases without the increased bronchial blood flow seemed due to bronchial asthma of long duration. By contrast, the one case (T.Ka.) who showed the slightly increased bronchial blood flow had no history of bronchial asthma, but had suffered from chronic bronchitis for many years.

Pulmonary neoplasms — A significant increase in bronchial blood flow, ranging from 0.64 l./min to 0.81 l./min, from 12.2 per cent to 22.7 per cent in the ratio to the right ventricular ooutput, was obtained in four of five cases with bronchogenic pulmonary carcinoma.

Of three who had metastatic lung cancer from carcinoma of the thyroid gland, two failed to show a significantly increased bronchial blood flow. The other case (C.T.) with an episode of pneumonia two months before showed the high value of 2.36 l./min.

Oxygen Saturation and Venous Admixture

Generally speaking, a decrease in arterial oxygen saturation and an increase in venous admixture ratio were frequent in pulmonary emphysema, while they occurred in only a few cases of bronchiectasis, pulmo-

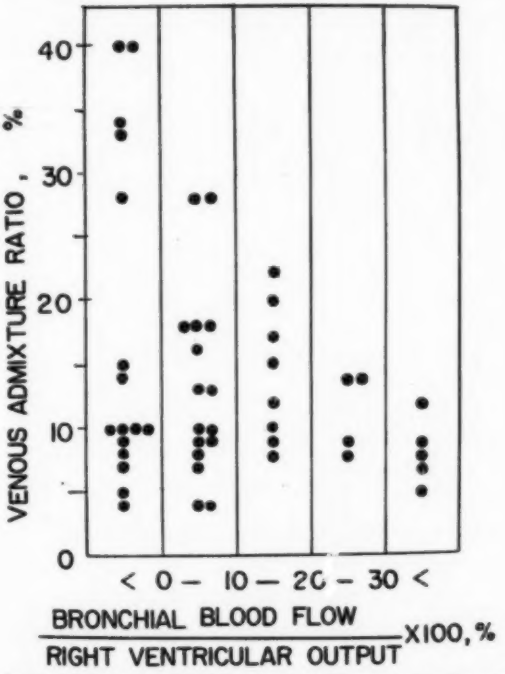

FIGURE 2: Relation between bronchial blood flow and venous admixture ratio in patients with various pulmonary diseases.

TABLE 2—BRONCHIAL BLOOD FLOW, ARTERIAL OXYGEN SATURATION, VENOUS ADMIXTURE AND PULMONARY ARTERY PRESSURE IN 50 PATIENTS WITH VARIOUS CHRONIC PULMONARY DISEASES

Subject	Ventricular Output Left	Ventricular Output Right	Bronchial Blood Flow	Br.B.F./R.V.O.	Arterial Oxygen Saturation	Venous Admixture Ratio	Pulmonary Artery Pressure Systolic	Pulmonary Artery Pressure Diastolic	Pulmonary Artery Pressure Mean
	1/min	1/min	1/min	per cent	per cent	per cent	mmHg	mmHg	mmHg
Bronchiectasis									
C.S.	5.57	5.11	0.46	9.0	97	4	—	—	—
M.T.	6.60	6.44	0.20	3.3	91	18	22	11	14
S.A.	7.90	7.28	0.62	8.5	96	8	26	12	16
A.T.	7.25	6.54	0.71	10.8	94	17	29	15	19
K.I.	6.59	5.92	0.67	11.3	95	15	21	9	16
T.K.	7.10	6.71	0.39	5.8	88	28	23	12	15
H.S.	9.31	7.56	1.75	23.1	94	14	19	9	14
K.S.	10.95	4.41	6.45	148.3	98	5	25	10	12
Pulmonary Tuberculosis									
T.I.	7.40	7.43	— 0.03	— 0.4	93	14	30	17	22
M.H.	9.58	10.19	— 0.61	— 6.0	93	10	26	10	14
K.S.	8.19	5.60	2.59	46.3	94	12	30	12	20
A.A.	8.43	6.08	1.34	22.3	92	14	40	20	25
S.O.	7.00	7.30	— 0.30	— 4.1	95	15	22	8	13
R.Y.	5.72	5.80	— 0.08	— 1.4	95	4	25	11	18
R.K.	7.86	7.94	— 0.08	— 1.0	81	40	35	15	27
K.M.	4.46	4.40	0.06	1.4	84	28	22	11	15
Silicosis									
T.Y.	4.75	4.68	0.07	1.5	94	7	21	5	15
J.O.	4.20	4.14	0.06	1.4	96	9	21	5	10
To.K.	5.59	6.11	— 0.52	— 8.5	97	10	18	7	11
M.Y.	6.43	6.08	0.35	5.7	94	13	23	8	12
T.T.	4.22	4.33	— 0.11	— 2.5	97	8	27	10	18
M.T.	8.70	8.94	— 0.24	— 2.9	95	10	29	8	13
T.I.	3.70	3.85	— 0.15	— 3.9	95	5	38	14	19
S.H.	4.29	2.97	1.32	44.5	93	9	32	16	22
C.F.	3.97	4.09	— 0.12	— 2.9	94	10	23	7	14
S.Y.	8.54	7.67	0.87	11.3	94	8	—	—	18
Ta.K.	6.88	6.01	0.87	14.4	92	12	20	6	13
T.O.	4.78	4.93	— 0.15	— 3.0	96	7	31	11	20
C.Y.	7.71	6.85	0.86	12.5	96	10	35	14	22
M.K.	7.78	5.00	2.78	55.6	93	8	28	15	20
Pulmonary Abscess									
H.S.	5.45	5.40	0.05	0.9	99	3	21	13	19
M.Y.	8.90	8.81	0.09	1.0	96	10	27	12	20
B.O.	8.19	7.63	0.56	7.5	95	9	30	14	19
K.W.	7.66	7.09	0.57	8.0	93	10	20	8	12
Pulmonary Emphysema									
K.U.	4.12	4.52	— 0.40	— 8.8	89	33	29	15	22
T.Kr.	2.89	3.17	— 0.28	— 8.8	84	28	26	14	17
S.Y.	6.32	6.85	— 0.53	— 7.7	96	9	32	15	21
S.Sm.	3.46	3.69	— 0.23	— 6.2	71	34	42	14	24
H.K.	4.98	4.86	0.12	2.5	91	18	21	9	13
S.Sa.	5.57	5.26	0.31	5.9	—	—	29	14	22
J.S.	4.39	4.09	0.30	7.3	93	13	23	11	16
T.Ka.	5.46	4.84	0.62	12.8	88	22	28	16	19
Pulmonary Neoplasms									
K.S.	6.30	5.97	0.33	5.5	92	18	27	8	16
Y.S.	5.89	5.25	0.64	12.2	88	20	18	8	12
D.I.	5.17	4.36	0.81	18.6	91	9	33	15	22
F.S.	4.06	3.35	0.71	21.2	94	9	34	15	22
K.Su.	4.33	3.53	0.80	22.7	95	8	36	16	22
K.Si.	7.13	7.41	— 0.28	— 3.8	84	40	25	10	15
K.W.	6.90	6.35	0.55	8.7	92	16	25	13	20
C.T.	10.15	7.79	2.36	30.3	96	7	21	10	13

nary tuberculosis and pulmonary neoplasms. None of the cases of silicosis or pulmonary abscess showed a significantly decreased arterial oxygen saturation or increased venous admixture ratio. The relations between bronchial blood flow and arterial oxygen saturation and between bronchial blood flow and venous admixture ratio are shown in Figs. 1 and 2. In these figures it is clearly demonstrated that arterial oxygen saturation and venous admixture ratio are maintained near the normal value when the bronchial blood flow increases.

Pulmonary Artery Pressure

The systolic, diastolic and mean pressures in the pulmonary artery are set out in Table 2. Although there was no case whose mean pulmonary artery pressure was more than 30 mm Hg, most of the patients studied showed slightly or moderately elevated pulmonary arterial pressure. However, no correlation was found between the bronchial blood flow and the mean pulmonary artery pressure (Fig. 3). Normal pulmonary artery pressure was frequently observed even in the cases with an extremely large bronchial blood flow.

Systemic Blood Pressure and Heart Size on Teleroentgenogram

Systemic blood pressure and four indexes for evaluating enlargement of the heart by teleroentgenogram are shown in Table 3. The systemic pressure was almost normal in all cases studied. Enlargements of the

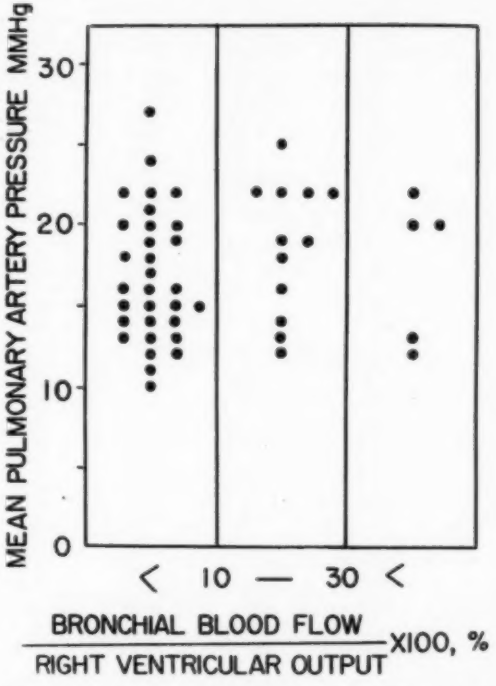

FIGURE 3: Relation between bronchial blood flow and mean pulmonary artery pressure in patients with various pulmonary diseases.

TABLE 3—SYSTEMIC BLOOD PRESSURES AND MEASUREMENTS OF HEART SIZE ON TELEROENTGENOGRAM

Subject	Systemic Pressure Systolic	Diastolic	Indexes for Evaluating Heart Size on Teleroentgenogram Trans. Dia. (Ratio to Pred.)	Card-Th. R.	Front. Area (Ratio to Pred.)	L x B / H x W
	mmHg	mmHg	per cent	per cent	per cent	per cent
Bronchiectasis						
C.S.	120	62	+10.6	44.7	+ 1.8	18.4
M.T.	132	70	− 8.7	39.7	−12.6	18.7
S.A.	128	82	+ 3.6	42.6	+ 5.7	20.4
A.T.	130	98	− 4.3	39.3	+ 3.0	18.9
K.I.	132	88	+ 7.1	48.0	+15.7	20.2
T.K.	106	64	− 3.5	40.0	+ 5.3	17.5
H.S.	112	70	+18.0	54.0	+34.3	28.3
K.S.	130	72	+25.0	50.9	+51.0	27.8
Pulmonary Tuberculosis						
T.I.	134	84	+ 6.2	48.0	+44.8	31.9
M.H.	150	110	+ 2.4	47.3	+12.9	25.5
K.S.	122	76	+ 4.2	48.1	+41.6	28.5
A.A.	130	65	− 6.8	42.3	+27	21.9
S.O.	120	80	+13.0	48.2	+27.8	25.1
R.Y.	127	74	−15.3	38.9	− 4.1	21.2
R.K.	96	61	± 0	42.9	± 0	18.4
K.M.	126	70	− 2.5	45.2	+ 8.2	22.9
Silicosis						
T.Y.	120	86	+ 3.4	43.6	+16.5	23.8
J.O.	126	78	+ 2.9	40.4	− 1.1	19.1
To.K.	120	60	+18.5	48.2	+25.5	21.9
M.Y.	130	70	+ 5.7	40.7	+11.0	20.2
T.T.	110	60	+ 9.1	44.6	+26.0	23.7
M.T.	130	82	+24.6	51.6	+40.9	26.4
T.I.	104	70	− 5.2	38.6	+ 1.8	20.4
S.H.	120	70	+39.4	55.8	+26.0	25.3
C.F.	150	90	+20.0	48.0	—	27.2
S.Y.	116	80	− 9.1	38.7	− 0.9	20.2
Ta.K.	120	80	− 1.9	36.2	+33.3	21.9
T.O.	110	84	+12.8	43.9	+50.0	25.5
C.Y.	136	92	± 0	43.1	− 6.9	19.7
M.K.	134	72	+ 2.8	39.3	+20.4	21.3
Pulmonary Abscess						
H.S.	138	78	+ 7.4	49.1	+21.1	24.1
M.Y.	130	75	+ 4.2	44.6	+12.4	20.8
B.O.	130	72	+16.8	51.8	+14.3	28.2
K.W.	128	88	+16.4	47.2	− 6.4	19.2
Pulmonary Emphysema						
K.U.	106	62	+ 4.3	44.4	+ 4.4	19.1
T.Kr.	126	80	+ 9.6	44.7	+ 9.5	20.7
S.Y.	120	66	+ 7.8	48.1	+15.3	21.7
S.Sm.	110	60	+ 4.0	41.2	+ 5.8	18.4
H.K.	118	94	+ 7.1	46.2	+ 8.2	19.8
S.Sa.	155	105	− 7.4	41.8	+14.1	21.6
J. S.	146	100	+14.7	48.9	+29.2	23.1
T.Ka.	154	94	+ 8.5	40.4	+ 8.6	17.5
Pulmonary Neoplasms						
K.S.	110	68	+21.0	55.4	+49.5	35.5
Y.S.	128	90	+35.1	53.6	+48.6	24.8
D.I.	110	60	− 7.8	34.6	− 4.4	17.1
F.S.	116	64	−13.2	37.1	+ 9.3	23.3
K.Su.	140	100	+19.3	48.2	− 3.1	17.8
K.Si.	114	57	± 0	45.3	− 1.0	22.8
K.W.	145	88	+ 4.3	43.7	+ 7.9	21.7
C.T.	124	72	+38.4	57.5	+75.7	30.3

TABLE 4—COMPARISON BETWEEN PULMONARY ARTERY MEAN PRESSURE AND HEART SIZE ON TELEROENTGENOGRAM

Pulmonary Artery Mean Pressure mm.Hg.	No. of Cases		Trans. Dia. per cent	Card-Th. R. per cent	Front. Area per cent	$\frac{L \times B}{H \times W}$ per cent
<16	23	Mean	+11.3	46.9	+21.7	23.8
		S.D.	±12.1	± 4.6	±21.5	± 4.3
17-20	14	Mean	+ 3.3	43.3	+15.1	22.3
		S.D.	± 8.5	± 4.1	±15.1	± 3.1
>21	12	Mean	+ 3.8	43.9	+ 8.5	21.3
		S.D.	±13.6	± 5.3	±14.4	± 3.9

heart were the most frequently found in frontal area of the four indices, and they were the least in pulmonary emphysema among various chronic pulmonary diseases. All patients had had no sign and no history of heart failure and systemic hypertension. Comparisons of the indexes of heart size to pulmonary artery mean pressure and bronchial blood flow are indicated in Table 4 and 5. Table 4 shows that the four indexes are rather greater in the group with normal mean pulmonary artery pressure (< 16 mm. Hg.) than in the groups with slightly or moderately elevated pulmonary artery pressure. Table 5 shows that the enlargement of heart size is marked in the group with the largest bronchial blood flow (> 30 per cent of right ventricular output), although the enlargement in the group in which bronchial blood flow is 10 to 30 per cent are less than those in the group in which it is less than 10 per cent. Thus, it is clear that the enlargement of the heart does not depend upon elevation of pulmonary artery pressure, but is connected with the increase in bronchial blood flow. However, there was no abnormal finding in electrocardiogram in spite of such a considerable enlargement of the heart.

Discussion

1) The interpretation of the present results in the light of previous observations by others.

The present study in subjects with various chronic pulmonary diseases has confirmed that an increment of bronchial blood flow varies considerably depending on the diseases. These results may merit assessment first in connection with anatomic evidences by many investigators and secondly as a basis for disclosing the mechanism of development of the bronchial artery.

Among various chronic pulmonary diseases, bronchiectasis has been indicated as the most prominent disease in respect to the development of the bronchial artery and the broncho-pulmonary anastomoses. The present study reveals a significant increase in bronchial blood flow in four cases with bronchiectasis, though the increase is suspicious in other four cases. These results are in accordance with the anatomic observations reported.[1,3,4,5] Fishman et al.[11] demonstrated "effective" collateral blood flows

TABLE 5—COMPARISON BETWEEN BRONCHIAL BLOOD FLOW AND HEART SIZE ON TELEROENTGENOGRAM

$\frac{Br.B.F.}{R.V.O.} \times 100$ per cent	No. of Cases		Trans. Dia. per cent	Card-Th. R. per cent	Front. Area per cent	$\frac{L \times B}{H \times W}$ per cent
<10	32	Mean	+ 6.4	45.2	+14.1	22.6
		S.D.	± 8.9	± 3.8	±15.6	± 3.9
10-30	13	Mean	+ 3.8	43.0	+11.0	21.0
		S.D.	±11.8	± 6.3	±16.7	± 3.1
>30	5	Mean	+21.9	50.3	+42.9	26.6
		S.D.	±16.1	± 6.4	±18.9	± 3.1

in two cases with bronchiectatic and cystic disease of the lung, but these blood flows did not exceed 5 per cent of the total pulmonary blood flow and appear to be somewhat lower than the present results. This discrepancy seems due to the fact that their method measures only the "effective" collateral blood flow, i.e. a component of the total collateral blood flow which reaches the alveolar capillary surface of the lung to participate in gas exchange, while the present one measures the whole of the pulmonary collateral flow.

It might be considered that the development of the bronchial arteries or pulmonary collateral vessels depends on the extent and character of lesion. In fact, the results in bronchiectasis revealed an increase in bronchial blood flow parallel to the extent of the lesion, and the increase tended to be more striking when the lesion was cystic than cylindrical in character. In view of the present observation, however, that the lesion in the former case was generally found to be more extensive than in the latter, nothing can be answered to the question which one of these, the extent or the character, should give rise to the increase in bronchial blood flow.

In a case (S.S.) with extensive bilateral bronchiectasis a surprisingly large value of bronchial blood flow, 6.46 lit./min. (148.3 per cent of right ventricular output) and 6.91 lit./min. (138.5 per cent of the right ventricular output) during breathing of ambient air and of 15.6 per cent oxygen, respectively, was obtained. This case has been suffering from unexplained exertional dyspnea and palpitation for many years and has had from time to time an attack of pneumonia. In physical examination his digits were clubbed but neither heart murmur nor cyanosis was present. A considerable enlargement of heart size was found on the teleroentgenogram as shown in Table 3, but the ECG did not show abnormality except left axis deviation. The pulmonary function studies revealed no abnormality. By what mechanism and from what cause the extremely large bronchial blood flow took place only in this case could not be explained in the present study. It is, however, likely to be presumed that a large amount of bronchial blood flow has made a contribution to the cause of the exertional dyspnea and palpitation in this case.

In pulmonary tuberculosis, Cudkowicz[6] confirmed that enlarged bronchial arteries were present in affected lungs and cavities had a rich bronchial blood supply, a finding also observed by Wood and Miller,[7] by radiographic and histological examinations. In the present study the two cases with extensive productive and fibrotic lesions, showing a significant increase in bronchial blood flow, are comparable with these anatomic observations. On the contrary, the other six cases with cavities, ectatic bronchi or so-called destroyed lung did not indicate the increased blood flow despite considerably extended tuberculous lesions. Wright[2] suggested, in a teleological view concerning the cause of the development of the bronchial arteries, that collagen proliferation in the lung, irrespective of the cause, demands a profuse arterial blood supply, and Cudkowicz[6] also presumed that both the infection and the tissue defences require the bronchial circulation for their blood supply. Although in the scope of the present study it is impossible to clarify by what mechanism or from what difference such a contrast arises in the two groups described above, the proliferative action in tissue seems to play a role in developing the bronchial circulation.

The results of measurements of bronchial blood flow in silicosis are generally in coincidence with the anatomic study in coal-worker's pneumoconiosis by Wells,[14] in which he observed that the development and dilatation of the bronchial arteries were not found in the cases with uncomplicated pneumoconiosis, but remarkably in the cases with tuberculous complication and massive formation. The contribution of the tuberculous complication to the development of bronchial blood flow, however, was not clearly demonstrated in the present study because of its minimal degree of the complication in most of our cases. It is of great interest that the result of the bronchial blood flow in simple silicosis is far different from that in massive formation, for the latter is expected to be accompanied with infection. It seems that the silicotic granulation tissue produced by only the chemical action of silica dust differs in its blood supply from that with the participation of the infection.

In pulmonary abscess, Marchand, Gilroy and Wilson[5] described that abscess lesions receive a blood supply from the bronchial arteries and a profuse broncho-pulmonary anastomosis is found near the lesions. The bronchial blood flow in four cases in the present study, however, failed to increase significantly. Especially is it of interest that the blood flow in a case (K.W.) was only 8.0 per cent of the right ventricular output in spite of the presence of active inflammatory lesions considerably extended. It seems, therefore, that the pulmonary collateral circulation in pulmonary abscess does not increase as greatly as anatomic observations indicate.

Differing from other pulmonary diseases, the changes of the bronchial vascular system in emphysematous lungs are of considerable interest, and also of importance in relation to etiologic factors of pulmonary emphysema. Cudkowicz and Armstrong[15] observed that obliteration of the intrapulmonary bronchial arteries is a common feature in pulmonary emphysema as a whole and the lesions in the lungs vary greatly according to the extent of the occlusion in the bronchial circulation. After that Crenshaw[16] led their concept to treatment of pulmonary emphysema. The results of measurements of bronchial blood flow in pulmonary emphysema seem to confirm such anatomic observations, since no significant increment of the bronchial blood flow was seen except in one case. However, it must be kept in mind that the pathologic process in the lungs of pulmonary emphysema is not always uniform, but complicated with

atelectasis, bronchiectatic changes, pulmonary infection and so on, so that the behavior of the bronchial arteries in emphysematous lungs are greatly changeable depending upon these complications.

It was pointed out by some investigators[1,2,7] that primary pulmonary neoplasms were associated with development of the bronchial arteries. The present study in the first five cases with malignant pulmonary neoplasms indicates that bronchogenic pulmonary carcinoma receives a profuse blood supply from the pulmonary collateral vessels. Although the bronchial blood flow in the first case (K.S.) was insignificant in the scope of the present study with the value of 5.5 per cent of the right ventricular output, in the other four cases it showed significantly increased values, ranging from 12.2 per cent to 22.7 per cent. On the contrary, two cases with metastatic tumor from carcinoma of thyroid gland did not indicate the increment of bronchial blood flow. This evidence supports the observations by Wood and Miller[1] and Cudkowicz and Armstrong,[7] who demonstrated proliferative changes in the bronchial arteries only in primary bronchogenic cancer. The last case (C.T.) with metastatic tumor, however, showed a large bronchial blood flow. This case had had an episode of pneumonia and a dense shadow on teleroentgenogram. It is, therefore, probable that the pulmonary infection has made a contribution to the increased bronchial blood flow in this case.

As described above, the increase in bronchial blood flow has been quite variable depending upon diseases and their degree. However, it is not always simple to clarify in what case and by what mechanism the development of the bronchial blood vessels is induced. In pulmonary stenosis or in dogs with pulmonary artery ligation, a decline in pulmonary blood flow and in pulmonary artery pressure was associated with an increment of bronchial circulation, as pointed out by anatomic and physiological observations.[8,10,11] Such a mechanism is accepted as a contributing factor to the development of the bronchial arteries under those conditions. It is also conceivable that obliterative endarteritis of the pulmonary arteries in the tuberculous lesions or compression of the pulmonary artery by silicotic nodules or bronchogenic cancer, reducing pressure and flow of the pulmonary artery in such lesions, induce a development of the bronchial artery. However, the development of the bronchial vascular system cannot be interpreted only by the same mechanism in chronic pulmonary diseases. In fact, the various aspects of the bronchial vascular system in chronic pulmonary diseases in the present study were considerably different from those in pulmonary stenosis, the bronchial blood flow having no relation to the decrease in the pulmonary artery blood flow and in the pulmonary artery pressure. Hence it appears to be important and necessary to consider the behavior of the bronchial vascular system in inflammatory lesions which are inevitable in the process of chronic pulmonary diseases.

In the present study an increase in bronchial blood flow has been found to be associated with the inflammatory lesions or pulmonary infections. It seems important that the well-oxygenated bronchial artery blood is supplied to the inflammatory lesions, where an arrest of pulmonary blood flow and a resultant local anoxia may be induced. Thus, the bronchial artery blood possibly serves not only for arresting the development of intermediate metabolic products of the inflammatory lesions, but also for supplying energy for the tissue reaction in the lesions, and it may become a promoting factor to the proliferative reaction. Here arises presumably the meaning of the bronchial blood as a healing mechanism to the inflammatory lesions.

2) The effects of the bronchial circulation on the respiratory function of the lung.

When a high-pressure circulation, the bronchial, comes into direct communication with the low-pressure pulmonary artery system, blood in the pulmonary artery is shunted from the diseased lung tissue where anastomoses exist into the normal parenchyma where oxygenation will sufficiently take place. Consequently, none of the venous blood in the pulmonary artery traverses non- or poor-ventilated diseased lung tissue, so that desaturation of the systemic arterial blood is prevented. Evidence for this shunting mechanism could be demonstrated during life by angiocardiography in patients with massive chronic pulmonary disease of one side.[4,17] In the present study, it has been clearly indicated that both arterial oxygen saturation and venous admixture ratio are maintained near the normal value in proportion as bronchial blood flow increases, although the both are frequently deviated far from their normality when the blood flow shows little or no increase. This effect of the bronchial circulation on the oxygenation in the lung is of great importance. This seems to solve some discrepancies, frequently observed clinically, between the arterial oxygen saturation and the severity of lung disease judged by fluoroscopic examinations.

On the other hand, in the cases with severely restricted pulmonary blood flow, as in tetralogy of Fallot, causing a large pulmonary recirculation of the poorly saturated arterial blood resulting from the intracardiac venous shunt, a vastly developed bronchial circulation is expected to make a contribution to gas exchange or oxygen demand for the whole body. It was reported by Bing et al.[9] that, in tetralogy of Fallot, the ratio of oxygen intake to minute ventilation was rather higher during exercise than that at rest in the cases with a profuse collateral circulation, while the ratio during exercise was much lower than that at rest in the cases without an increase of the collateral circualtion. This fact indicates that the relatively unsaturated blood of the pulmonary collateral vessels, entering the lungs in compensation for a restricted pulmonary blood flow, contributes to gas exchange with resultant increased pulmonary capillary blood flow. The situation is analogous to Blalock's operation for tetralogy of Fallot. In the present study, however, this contribution appears to be

insignificant at rest because of the absence of the arterial desaturation associated with increased bronchial blood flow. It should be, nevertheless, reflected that it plays a great role in the respiratory function of the lungs at certain anoxic states or on increased oxygen demand as during exercise.

3) The effects of the bronchial circulation on the pulmonary and systemic circulations

It is clear that the numerous anastomases between the bronchial arteries with high blood pressure and the pulmonary arteries with low blood pressure lead to increased peripheral resistance within the lung, significance of which in producing pulmonary hypertension, as suggested by Wood and Miller,[1] must be evaluated. Nevertheless, there was not found any correlation between bronchial blood flow and pulmonary artery pressure in the present study, and a normal pulmonary artery pressure was frequently obtained even in the cases with an extremely large amount of bronchial blood flow. This seems due to an enormous reserve capacity of the pulmonary capillary bed, which is adaptable to a high degree and even a fraction of it can accommodate an enormously increased flow without pulmonary arterial hypertension, as Liebow et al.[4] suggested. Cournand[17] reported observations on patients with patent ductus arteriosus in whom there was a flow from the aorta into the pulmonary artery of as much as 8 lit/min, without pulmonary hypertension. Also Storstein et al.,[18] in the series in patent ductus arteriosus, described that pulmonary hypertension was not observed even in two cases whose pulmonary blood flow was more than three times as much as the systemic blood flow, and no significant correlation was found between pulmonary blood flow and pulmonary artery pressure. These observations indicate that the communications of the pulmonary circulation with the systemic circulation must be very complicated and not imply an increase in pulmonary resistance against which the right ventricle has to work.

On the other hand, it is apparent that the burden of the bronchial circulation must fall on the left side of the heart, considering the course of the blood. The blood brought from the lung to the aorta is returned, largely via the bronchial vessels, directly to the left auricle without passing through the right side of the heart as all other blood in the aorta does. Consequently, the output of the two ventricles differs by the amount of the bronchial circulation, and the left ventricle has to always expell more blood than the right. This burden was suggested by Liebow et al.[4] and the present authors[10] previously as a possible account for the hitherto unexplained hypertrophy of the left ventricle frequently observed in cor pulmonale in the absence of systemic hypertension, but it has never been actually proved.

In the present paper, a relation has been found between bronchial blood flow and enlargement of the heart in the absence of systemic hypertension and in the lack of any correlation with pulmonary artery pressure. This fact demonstrates the burden of the bronchial circulation on the heart, possibly on the left ventricle. Then, the development of the bronchial vascular system and the resultant increase of the left ventricular output should be considered as important factors in causing left ventricular hypertrophy.

SUMMARY

1. Measurements of bronchial blood flow were performed by the dye dilution method in 50 patients with various chronic pulmonary diseases including bronchiectasis, pulmonary tuberculosis, silicosis, pulmonary abscess, pulmonary emphysema, and pulmonary neoplasms, and the influences of bronchial circulation on respiration and circulation were studied.

2. In bronchiectasis, the bronchial blood flow showed the greatest increase among these pulmonary diseases and a surprising large value was obtained in one case.

3. In six of eight cases with pulmonary tuberculosis, no increase in bronchial blood flow was observed, but in the other two significantly increased flow was found. In silicosis, the cases with simple silicotic nodules did not show increased flow, while the cases with massive densities proved the significantly increased flow. We were unable to clarify the participation of tuberculous complication to the development of the bronchial collateral vessels.

4. Seven of eight cases with pulmonary emphysema did not indicate any increment in bronchial blood flow, but one with long-standing chronic bronchitis showed slightly increased flow. In pulmonary abscess the increase was insignificant in all four cases.

5. In pulmonary neoplasms, four of five cases with primary bronchogenic carcinoma showed increased bronchial blood flow, while two with metastatic pulmonary tumor did not show this increased flow. However, one case of metastatic lung cancer with an episode of pneumonia showed a large increase in bronchial blood flow.

6. From these results it was deduced that pulmonary infection is a contributing and determining factor in the development of the bronchial vessels.

7. When the bronchial blood flow was increased, irrespective of the cause, oxygen saturation and venous admixture ratio were maintained near the normal value. On the other hand, heart size on teleroentgenogram was enlarged in the cases with greatly increased bronchial blood flow, in the absence of systemic hypertension and without correlation with the elevation in pulmonary artery pressure.

RESUMEN

1. Se llevaron a cabo medidas del flujo bronquial sanguíneo, usando el método de la dilución de colorante, en 50 enfermos con varios padecimientos crónicos incluyendo: bronquiectasia, tuberculosis pulmonar, silicosis, absceso pulmonar, enfisema pulmonar y neoplasias pulmonares. Además se estudió la influencia de la circulación bronquial en la respiración y sobre la circulación.

2. En la bronquiectasia el flujo bronquial mostró el aumento mayor entre estas enfermedades pulmonares y un resultado sorprendentemente elevado se obtuvo en un caso.

3. En seis de los ocho casos con tuberculosis pulmonar, no hubo aumento del flujo sanguíneo bronquial pero en los otros dos el aumento era significativo. En silicosis: los casos con nódulos silicóticos simples no mostraron aumento del flujo sanguíneo bronquial en tanto que los casos con densificaciones muy voluminosas se encontró un aumento importante. No pudimos aclarar la participación que tenía la complicación tuberculosa en el desarrollo de los vasos colaterales.

4. Siete, de ocho casos, con enfisema pulmonar no indicaron un incremento en el flujo sanguíneo bronquial, pero un con bronquitis crónica de larga duración, mostró aumento ligero.

En el absceso pulmonar el aumento fué insignificante en todos los 4 casos.

5. En las neoplasias pulmonares, cuatro de cinco casos con carcinoma bronquiogénico primitivo, mostraron aumento del flujo sanguíneo bronquial, en tanto que dos con tumores metastásicos no mostraron ese aumento.

6. Según estos resultados se deduce que infección pulmonar es un factor determinante y adyuvante en el desarrollo de los vasos bronquiales.

7. Cuando el flujo sanguíneo bronquial aumentó, por [illegible]quier causa, la saturación de oxígeno y la relación de la oxigenación venosa se ma[illegible] alrededor de lo normal.

Por otra parte, el tamaño del corazón según la teler[illegible]ografía, estaba aumentado en los casos con aumento considerable del flujo sanguí[illegible]o bronquial, en ausencia de hipertensión general y sin relación con la elevación en la presión arterial pulmonar.

RESUMÉ

1. L'auteur a pratiqué des mesures du débit bronchique par la méthode des dilutions colorées chez 50 malades atteints de diverses maladies pulmonaires chroniques: bronchectasies, tuberculose pulmonaire, silicose, abcès du poumon emphysème pulmonaire et néoplasies pulmonaires; l'influence de la circulation bronchique sur la respiration et la circulation générale furent étudiées.

2. Dans la bronchectasie, le débit sanguin bronchique montra la plus grande augmentation de toutes ces affections pulmonaires, et dans un cas le chiffre obtenu fut étonamment élevé.

3. Dans six des huit cas de tuberculose pulmonaire, il n'observa pas d'augmentation du débit sanguin bronchique, mais dans les deux autres, il trouva un débit nettement augmenté. Dans la silicose, dans le cas de simples nodules silicotiques il n'y eut pas d'accroissement du débit, tandis que les opacités massives montrèrent un débit nettement augmenté. Il n'a pas été capable d'éclaircir le rôle de la tuberculose dans le développement des vaisseaux bronchiques collatéraux.

4. Sept des huit cas atteints d'emphysème pulmonaire ne montrèrent aucun accroissement du débit sanguin bronchique, mais un cas de bronchite chronique durant depuis longtemps donna un débit légèrement augmenté. L'augmentation fut insignifiante dans les quatre cas d'abcès du poumon.

5. Dans les néoplasies pulmonaires, quatre des cinq cas atteints de cancer bronchique primitif montrèrent une augmentation du débit sanguin bronchique, tandis que deux atteints de tumeur pulmonaire métastatique ne montrèrent pas cette augmentation. Cependant, un cas de cancer pulmonaire métastatique avec un épisode de pneumonie montra une importante augmentation du débit sanguin bronchique.

6. D'après ces résultats, on put déduire que l'infection pulmonaire est un facteur adjuvant et déterminant dans le développement des vaisseaux bronchiques.

7. Quand il existait une augmentation du débit sanguin bronchique, quelle qu'en soit la cause, la saturation oxygénée et le taux du mélange veineux demeuraient proches de la valeur normale. D'un autre côté, les dimensions cardiaques se montrèrent radiographiquement agrandies dans les cas où il y eut une grande élévation du débit bronchique, en l'absence de toute hypertension artérielle et sans qu'il y ait un rapport avec l'élévation de la pression artérielle pulmonaire.

ZUSAMMENFASSUNG

1. Bestimmungen des bronchialen Blutzirkulation wurden durchgeführt mittels der Farbstofflösung-Technik an 50 Kranken mit verschiedenen chronischen Lungenkrankheiten einschliesslich Bronchiektasie, Lungentuberkulose, Silikose, Lungenabszess, Lungenemphysem und pulmonalen Neoplasma. Es wurden ausserdem die Einflüsse der bronchialen Zirkulation aus Atmung und Kreislauf untersucht.

2. Bei Bronchiektasen zeigte die bronchiale Blutzirkulation den größten Anstieg von allen erwähnten Lungenkrankheiten, und in einem Fall ergab sich ein überraschend hoher Wert.

3. Bei 6 von 8 Fällen von Lungentuberkulose wurden keine Zunahme der bronchialen Blutzirkulation festgestellt; aber in 2 Fällen fand sich eine beträchtliche Erhöhung. Bei der Silikose zeigten die Fälle mit einfachen silikotischen Knötchen keine vermehrung der Durchströmung, während die Fälle mit massiven Verschattungen wesentlich erhöhte Werte aufwiesen. Wir waren außerstande, den Anteil der Suberkulösen Komplikation an der Entwicklung der bronchialen, Kollateralgefäße zu klären.

4. 7 von 8 Fällen von Lungenemphysem hatten keine für ein Ansteigen der bronchialen Zirkulation; lediglich ein Fall mit lange bestehender chronischer Bronchitis ergab eine etwas verstärkte Durchströmung. Beim Lungenabszess war die Zunahme in allen 4 Fällen unbedeutend.

5. Beim Lungentumor zeigten 4 von 5 Fällen von primären Bronchuscarzinom eine erhöhte bronchiale Blutzirkulation, wo hingegen 2 Fälle von Lungenmetastasen eine solche nicht zeigte. Allerdings fand sich in einem Fall von metastatischem Lungenkrebs mit einer interkurrenten Pneumonie eine starke Erhöhung der bronchialen Zirkulation.

6. Aus diesen Ergerbnissen wurde die Folgerung gezogen, daβ ein pulmonaler Infekt ein mitwirkender und bestimmender Faktor ist bei der Entwicklung der Bronchialgefäße.

7. Wenn die bronchiale Blutzirkulation verstärkt war, so hielten sich-unbeschadet der Ursachen die Sauerstoffsättigung und das venöse Mischungsverhältnis in ungefähr normaler Höhe. Andererseits war der Herzumfang auf Röntgenfernaufnahmen vergrößert in Fällen mit stark erhöhter bronchialer Blutzirkulation, ferner beim Fehlen einer Hypertension im groβen Kreislauf und ohne Beziehung zur Erhöhung des pulmonalen arteriellen Druckes.

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Fundamental Studies on Maintenance of the Circulation in Cardiac Asystole by the Mechanocardiac Pulsator*

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Cardiac asystole which manifests itself as a ventricular fibrillation or cardiac standstill is an accident occurring in approximately 0.1 per cent of all surgical interventions.[5] It has been reported that 87 per cent of cardiac arrests occur in the operating room.[6]

In many medical institutions of the world, the customary approach to the problem is time consuming and conservative. All too frequently transparietal intracardiac injections of analeptics are used and are nearly always unsuccessful. If by chance they do restore heart function, it is doubtful as to whether the heart was in arrest in the first place. The alternative approach which is gaining popularity with surgeons with respect to cardiac resuscitation is that heart massage should be the exclusive treatment. In the event of a mistaken diagnosis of cardiac asystole, the intervention would still be justified as the better choice of two evils. Unfortunately, it is not always possible to restore adequate circulation of the blood before anoxia has done irreparable damage to the brain. It is now universally accepted that the critical time period whereby circulation can be detained without permanent damage to the central nervous system is four minutes. Statistical studies done by various authors[3,6] concerning this time rule has proved that survival with or without neurological sequelae is above 80 per cent when the circulation has been promptly restored. Failing to restore circulation within this time limit brought the survival rate down to approximately 30 per cent, mortality increasing for every extra minute of time that was delayed.

It is understood that survival is not assured even when massage is done within the four-minute period. There are numerous factors which will determine the outcome of cardiac massage, such as the state of the heart itself, whether it be in failure, intoxicated by overdosage of anesthetics, anoxia, etc. Furthermore, the technique of the operator doing the massage and the maintenance of adequate blood pressure by intravenous infusions of vasoconstrictors should be given consideration.

The object of this paper is to study primarily the methods of heart massage and to give some thought concerning the use of vasoconstrictors and plasma expanders as ancillary agents to maintain adequate blood flow during cardiac asystole.

The primary cause for inadequate blood flow during manual massage is incorrect technique and fatigue of the operator. This sufficed to justify a study of the alternative possibilities to overcome the varying performance of the human factor in play. To this purpose cardiac mas-

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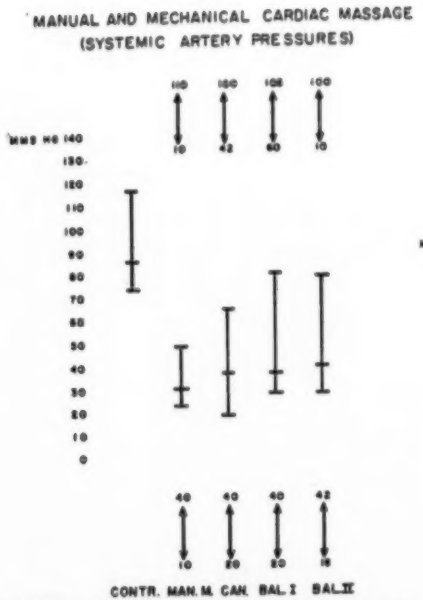

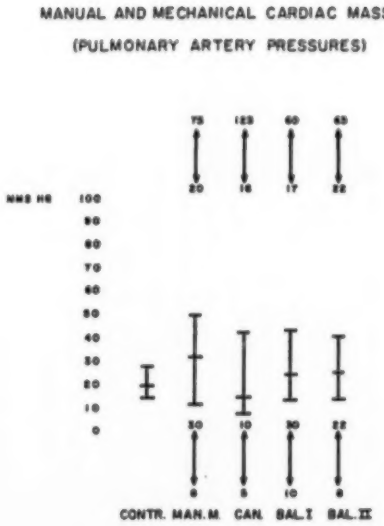

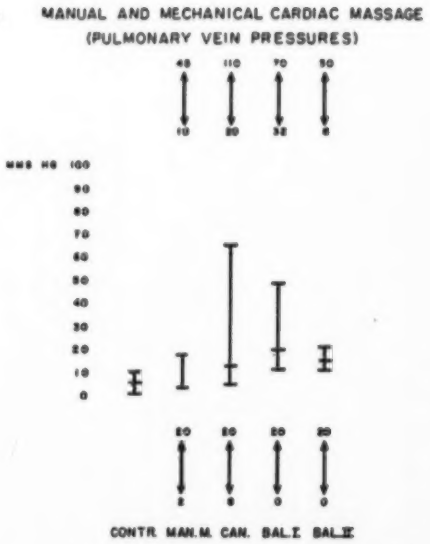

FIGURE 1A: Key to abbreviations: (Contr.) controls; (Man. M.) manual massage; (Can.) rubber flanged cannula; (Bal. I) balloon; (Bal. II) mantled balloon. Graphic results of the systemic arterial pressures obtained in 28 mongrel dogs weighing 10-16 kilos during cardiac compression compared with their original control values. Above are shown systolic pressure variations. In the middle: average systolic, mean and diastolic pressures. Below are the diastolic pressure variations. Note improved pressures in Bal. I and Bal. II compared with those in manual massage and cannula experiments.

FIGURE 1B: Key to abbreviations: (see Fig. 1A). Graphic results of the pulmonary artery pressures obtained in the same way as described in Fig. 1A. Above are shown systolic pressure variations. In the middle: average systolic, mean and diastolic pressures. Below are the diastolic pressure variations. Note above the high range of systolic pressure variations in the cannula experiments, with (middle) an average mean below that of the control. Note also the high pulmonary artery mean with manual massage.

FIGURE 1C: Key to abbreviations: (see Fig. 1A). Graphic results of the pulmonary vein pressures obtained in the same way as described in Fig. 1A. Above are shown systolic variations. In the middle: average systolic, mean and diastolic pressures. Below are the diastolic pressure variations. Note the comparatively low systolic variations of pressure with manual massage and the balloons. Note also that the average systolic pressures with manual massage and in the experiments done with Bal. II were much lower than those obtained with the cannula and Bal. I.

sage by mechanical means had stimulated the endeavors of two research teams outside of this country[1,2] apart from our own.

It was considered worthy of speculation to further the studies reported by Bencini and Parola on pneumomassage of the heart. Particular emphasis was to be placed on the study of the hemodynamic response in the systemic and pulmonary circulation with a purpose in view of making possible technical improvements.

Experimental Methods

The general outlay for experimentation was divided into three parts: a) to continue studies on pneumomassage of the heart; b) experimentation on heart compression by the intermittent inflation of a balloon in the pericardial sac placed behind the left ventricle; c) similar experiments with a balloon included in a mantle of nylon cloth; d) experiments on manual heart massage to compare with experiments A, B, and C.

A new apparatus was designed to obtain intermittent positive pressure by the use of a Y tube or modified Venturi tube with the addition of a pop-off valve, closed intermittently by a cam rotating on a shaft driven by an electric motor (Figs. 2A, and 2B). The cycles of pressure were so regulated by the adjustable cam as to produce a one-third positive or systolic and a two-thirds negative or diastolic phase, the latter having a negative pressure of −3 to −5 mm. Hg.

A cannula with a circular rubber flanged end (Figs. 3D, and 3D') was devised for inflating the pericardial space.

Introduction of the cannula into the pericardial sac was made easier by raising the pericardium from the myocardium by suction. This was done with a double-walled stainless steel tube (Figs. 3C, and 3C') with the intermural space connected to a vacuum pump via a side arm. The suction end was then applied to the pericardium through the central lumen of the suction tube and a stainless steel tube was passed with a circular hollow ground cutting edge at one end (Figs. 3E, and 3E'). Alternating rotary movements cut out a round piece of pericardium. The cutting tube was then withdrawn and the lubricated cannula introduced flange forward down the lumen of the sucker tube (Figs. 3C, and 3C') until the flange spread out under the pericardium securing the cannula in place. The opposite end of the cannula was then attached to a polyethylene tube connected to the Venturi tube. The air pressure in the cannula intermittently inflated the pericardial sac and was transmitted to the walls of the heart collapsing the chambers, thus causing the blood to flow into the systemic and pulmonary circulation.

In this paper, a total of 55 experiments on mongrel dogs were done and distributed in the following order: (A) 36 with the cannula (pneumomassage); (B) 7 with a balloon placed behind the left ventricle within the pericardial sac; (C) 8 with a mantled balloon placed as in B; (D) 4 with manual compression.

Experimental Procedure

Positive pressure ether-oxygen anesthesia was used for these experiments. Thoracotomy was done through the fifth interspace on the left or right side. The femoral artery, pulmonary artery and pulmonary

vein were catheterized with #P190 polyethylene tubing linked up to P23D strain gauges. All pressures were monitored on a five-channel Grass Polygraph recorder (Fig. 5). Cardiac asystole was produced with an electrical fibrillator-defibrillator apparatus, using 100 volt A.C. for fibrillation and 150-volt A.C. for defibrillation after completion of the experiment (Fig. 4). A venous cutdown was done in practically all the experiments for the infusion of vasoconstrictors and plasma expanders. During pumping, the ether was cut off and the dog received only oxygen by positive pressure respiration.

Experimental Results

(A) *Pneumomassage of the heart.* Thirty-six experiments were made in this group. To maintain an adequate systemic pressure it was found that the optimum positive pressure phase within the pericardial sac was

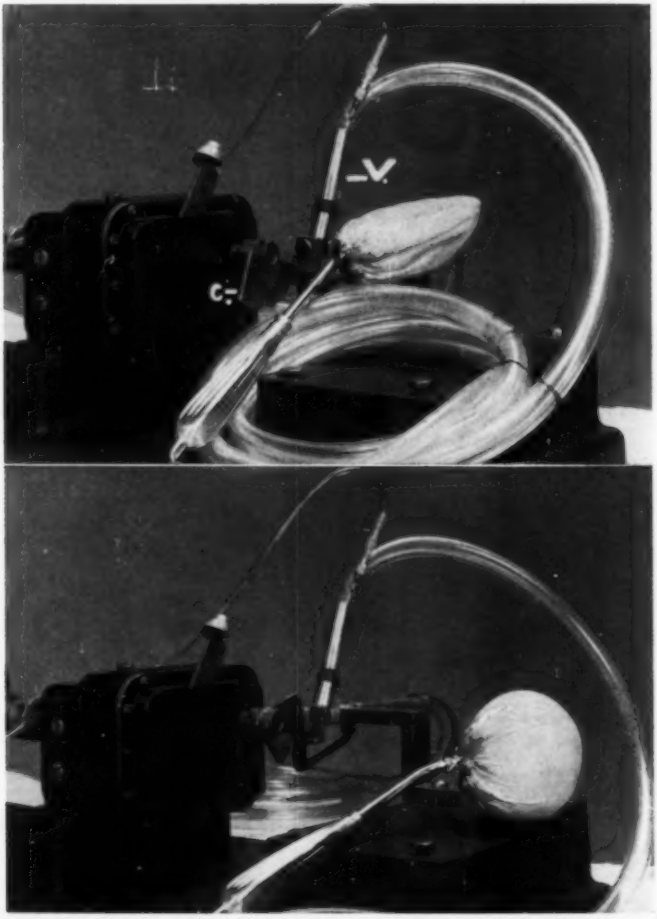

FIGURE 2A: Venturi tube (V) with cam (C) disengaged, producing the diastolic phase of the pump cycle. Note the collapsed mantled balloon on the cannula.
FIGURE 2B: Venturi tube with cam engaged producing the systolic phase of the pump cycle. Note distention of the mantled balloon.

120 mm. Hg. at 60-70 cycles/minute. The response to this pressure on the heart chambers in experiments that lasted 10 to 30 minutes gave the folowing average systolic, diastolic and mean pressures in mm. Hg.: Systemic artery 64/20-39, pulmonary artery 45/9-14 and pulmonary vein 67/7-15 (Figs. 1A, 1B and 1C above Can.)

Pressures were also taken in the thoracic inferior vena cava giving a range of 14/2 - 50/5 as compared with controls that ranged from 5/-2 to 30/15 mm. Hg.

Vasoconstrictors (adrenalin 0.1 per cent or Levophed 8/mil. sol. in 500 cc. D/W 5 per cent) were infused either into a peripheral artery or vein. Infusion into the artery gave a prompt elevation in blood pressure of 10-30 mm. Hg. which was sustained during five to ten minutes. The response following intravenous infusion was often less marked and less sustained, lasting two to five minutes after infusion was discontinued.

Plasma expander (Dextran) was found to increase the blood pressure when it was infused intravenously in massive doses varying from 1000 to 1500 cc. Response of the blood pressure with the use of Dextran was a rise in systemic blood pressure of approximately 10-30 mm. Hg. The

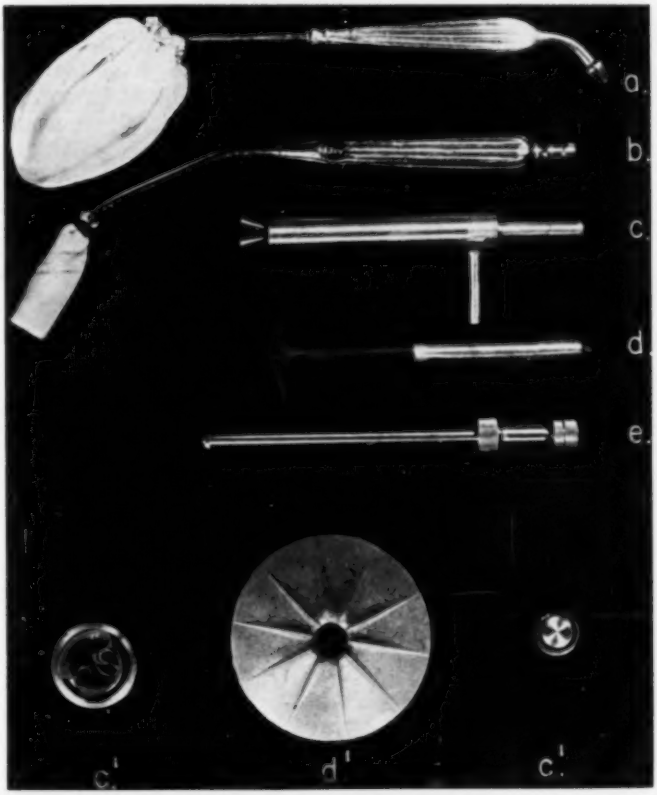

FIGURE 3: *Above-down:* (a) Bal. II; mantled balloon and cannula. (b) Bal. I, balloon and cannula. (c) suction tube with the rubber flanged cannula in the central lumen. (d) rubber flanged cannula. (e) calibrated hollow ground cutting tube.

use of Dextran intra-arterially showed no effect on the blood pressure. Plasma expander was discontinued in later experiments because it was found that its use contributed to high pressures in the vena cava (90/30 mm. Hg.), often higher than in the femoral artery. This situation was reversed when vasoconstrictors were subsequently infused intravenously. Pumping with the cannula introduced into the right side of the pericardial sac produced higher right ventricle pressures than when the cannula was placed on the left side. Right-side pumpings gave pressures of 140 - 150/25 in the right ventricle with a mean of 50 mm. Hg. This pressure was higher than the systemic which was 80/40 with a mean of 60 mm. Hg.

Pathology

Microscopic sections of the central and peripheral parts of the lung in these experiments showed: (a) mantle hemorrhages especially in the smaller pulmonary arteries; (b) massive hemorrhage of the lungs; (c) septal lymphangiectasis; (d) marked venous dilatation; (e) bleeding into the alveoli, and (f) intrapleural hemorrhage. It was consistently found that the mantle hemorrhages predominated in those experiments when pumping was done on the right side, whereas venous dilatation and congestion with veno-capillary hemorrhage predominated in lungs when the cannula was introduced on the left side of the pericardial sac. The cause of death in these experiments was attributed to cardio-respiratory insufficiency (anoxia) secondary to a low cardiac output during experimentation and severe damage to the lungs.

The survival rate in the 36 experiments after 10 to 30 minutes in asystole was as follows: two dogs were total survivors; two survived for 48 hours; three for 12 hours and one for four hours.

(B) *Mechanical heart compression by intermittent inflation of a balloon placed behind the left ventricle within the pericardial sac (Fig. 3B).*

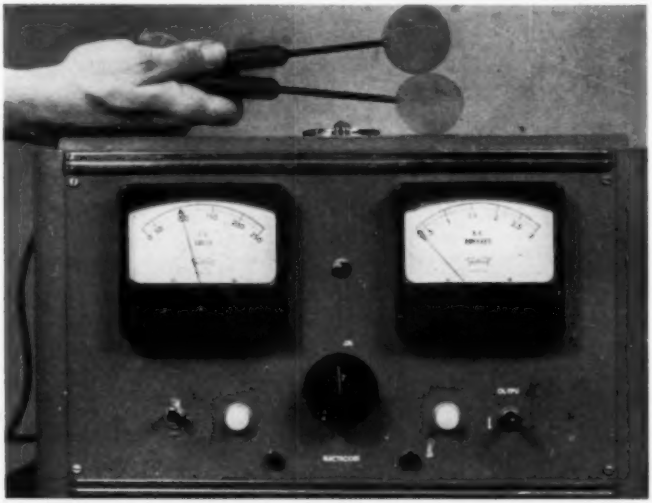

FIGURE 4: Fibrillator-defibrillator apparatus with blades.

Seven experiments were done in this group. Air pressure was conduced intermittently to a balloon also by the Venturi tube. Optimum pressure in the balloon was found to be 250 mm. Hg. at 60 cycles/minute. A high pericardiotomy was done at the level of the left auricular appendage and above the left phrenic nerve. The balloons were made from ⅝" Penrose tubing fixed to the end of a hockey stick-shaped cannula. This was introduced through the pericardiotomy and the balloon was placed behind the left ventricle. The pressure was projected directly against the left ventricle while the right ventricle was squeezed between the anterior surface of the pericardium and left ventricle itself (Figs. 6A and 6B).

The experiments lasted 4 to 30 minutes and gave the following average systolic, diastolic and mean pressures in mm. Hg.: Systemic artery 81/30-39, pulmonary artery 47/13-24 and pulmonary vein 50/12-21. (Figs. 1A, 1B and 1C above Bal. 1). Vena cava pressures were not monitored because experience in the previous experiments with the cannula led us to think that the low survival rate and lung damage was caused by an excessive pressure in the pulmonary artery and vein.

Pathology: Macroscopically the lungs appeared normal. Microscopic sections of the lungs of the dogs in these experiments gave no data suggestive of severe damage to the pulmonary vascular tree or alveoli due to pumping.

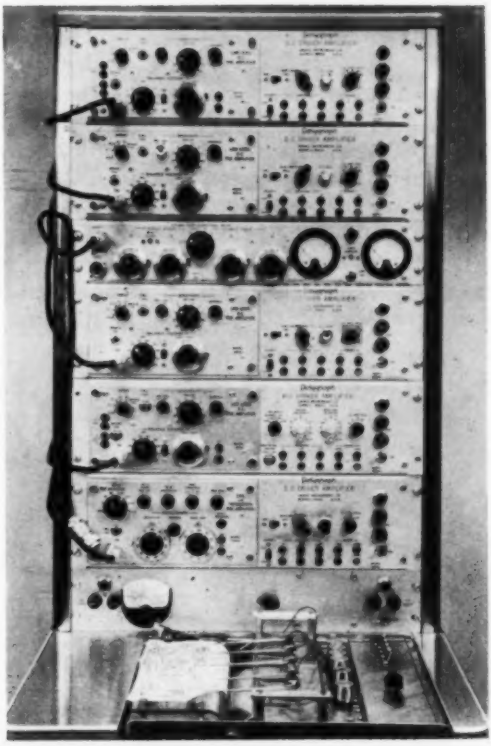

FIGURE 5: Grass polygraph pressure recorder.

Of this group, four dogs survived more than 12 hours. Two died of empyema a week later and one died the following day of pneumothorax due to a tear of the left lung during catheterization of the pulmonary vessels. One remained a total survivor.

(C) *Mechanical heart compression by* intermittent inflation of a mantled balloon also placed behind the left ventricle (Figs. 6A, 6B). The balloon used in this series of eight experiments was of similar construction as the one used in the previous experiment (Fig. 3A). Expansion of the balloon was limited by a mantle or pouch of nylon cloth when it was inflated. Thus the balloon acquired a spherical shape with increased tension. Expansion of the balloon toward the auricles was considerably reduced. The optimum pressures in this balloon ranged between 450 and 500 mm. Hg. with the same systolic/diastolic phase as in experiments (A) and (B).

The *results* obtained by pressure monitoring during the experiments which lasted from 3 to 65 minutes gave the following average systolic, diastolic and mean pressures in mm. Hg.: Systemic artery 80/31-41, pulmonary artery 41/14-25 and pulmonary vein 22/12-15. (Figs. 1A, 1B and 1C above Bal. 2).

Pathology: Macroscopic observations and microscopic sections revealed no damage to the lungs. Of the group, four dogs were total survivors, one died two days later, the remaining three died on the table of technical difficulties.

(D) *Manual cardiac compression.* The results of the three previous experiments described above were compared with the results of four experiments obtained by manual compression of the heart. Five surgeons participated in these experiments, two or more taking part on each of the four animals. Each surgeon massaged the heart for a period of three to five minutes, usually alternating the right and left hand. The operator was kept unaware of the effect that his cardiac resuscitation had on the pressures monitored.

The graphs of the pressure responses to manual compression of the heart were made by averaging the sum of the pressure curves in the

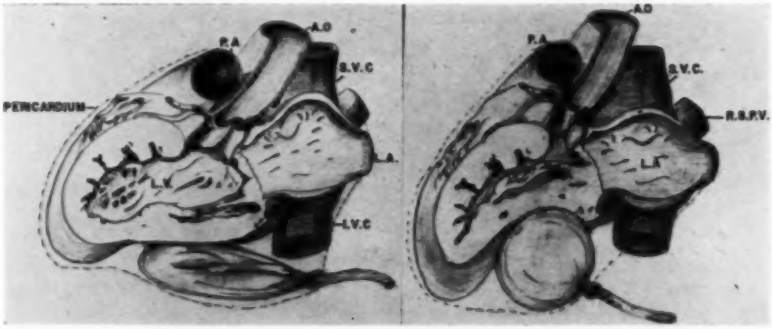

FIGURE 6A: Mantled balloon in the diastolic phase behind the left ventricle within the pericardial sac. Key to abbreviations: (L.A.) left auricle; (L.V.) left ventricle; (A.O.) aorta; (P.A.) pulmonary artery. FIGURE 6B: Mantled balloon in systolic phase (inflated) behind the left ventricle within the pericardial sac. Note the selective compression of the left ventricle. Key to abbreviations: (see Fig. 6A).

four experiments independent of the operator massaging. The *results* obtained gave the following average systolic, diastolic and mean pressures in mm. Hg.: Systemic artery 50/27-35, pulmonary artery 51/12-32 and pulmonary vein 19/6-6. (Figs. 1A, 1B and 1C Man. M.).

Discussion

Pneumomassage or heart massage by inflation of the pericardial sac with consequent compression of all the anatomical structures within the pericardium, was feasible because the pericardium has a high tensile resistance. This membrane withstood pressures of 350-500 mm. Hg. in dogs, and 600-1125 mm. Hg. in human cadavers (Bencini and Parola). The pressure in the pericardial sac was transmitted in inverse proportion to the thickness of the walls against which it compressed. For instance, the vena cava, compressed pulmonary veins and pulmonary artery were most compressible. This sequence was followed by the right ventricle and lastly the left which has the thickest wall. In other words, the anatomical condition is the reverse of that which is needed to maintain a good flow of blood from the venous system through the lungs to the systemic circulation. The following table which represents the percentage relationship between the average femoral artery, pulmonary artery and pulmonary vein mean pressures to the controls, was as follows:

	Mean Pressures	Surface exposed to pressure	Wall thickness
Femoral artery	44 per cent	Left Ventricle	+++
Pulmonary artery	50 per cent	Right Ventricle	++
Pulmonary vein	250 per cent	Left Atrium	+

One detail of interest (Figs. 1B, 1C and Can) is that the average pulmonary vein mean pressure is higher than that of the pulmonary artery. This abnormal response was attributed to be the cause of massive hemorrhage of the lungs which was evident macroscopically as a petechial pleural hemorrhage. A cut section of the lungs showed intense congestion and frothy fluid within the bronchi. Microscopic sections showed diffuse hemorrhage of the lungs and mantle hemorrhages.

With the abnormal pressure and pathology of the lungs in mind an hypothesis was contemplated to explain the hemodynamic paradox in the systemic and pulmonary circulation. It was thought that because the left ventricle was compressed less than the right, the cardiac output should be diminished and that with the right ventricle pressure above normal, the blood consequently pooled in the pulmonary vein and left atria. The last two act as a single chamber of thin walls receiving with each compression a back flow towards the lungs which may be responsible for the pulmonary venocapillary hemorhage. This situation was most evident when pumping was done on the left side. When pumping on the right side, pulmonary artery pressures increased over pulmonary vein pressures; in these cases mantle hemorrhages were most conspicuous. The experience accumulated in these experiments gave ample ground work for technical improvements to be made in mechanical heart compression. Some theoretical considerations were proposed, *i.e.*, (1) the pressure system should be more localized to the ventricles; (2) the left ventricle should be compressed more than the right and (3) the thin-walled structures should be spared.

It was thought that a balloon attached to the end of a cannula could qualify for this purpose if it were placed behind the left ventricle within the pericardial sac. In this way the left ventricle would receive the main impact from the intermittently expanding balloon. The right ventricle would secondarily receive a residual pressure through the interventricular septum, being compressed between the pericardium and the left ventricle (Figs. 6A, and 6B).

With these experiments, the percentage of the average mean pressures of the femoral artery, pulmonary artery and pulmonary vein against controls gave the following data:

	Mean pressures	
Femoral artery	44 per cent	(systolic 17 mm. Hg. higher than with the cannula (diastolic 10 mm. Hg. higher than with the cannula
Pulmonary artery	120 per cent	
Pulmonary vein	300 per cent	

These figures showed an increase of the pulmonary artery and pulmonary vein pressures when compared with the experiments of pneumomassage. Consulting Figs. 1B and 1C above Bal. 1. it was found that the average pulmonary artery means are higher than those of the pulmonary vein by 3 mm. Hg. This is an improvement although far from adequate. More survivors were obtained in this group and the lungs showed no pathological changes attributable to any acute vascular accident.

The new system of mechanical compression had some obvious defects: (1) the balloon expanded upwards compressing the left atria. This was revealed by the high

pressure response in the pulmonary vein; (2) the balloon expanded towards the pericardiotomy, finally bursting the pericardium; (3) balloons being made of rubber (like all elastic materials), if subjected to intermittent distention, produce heat, distend and then rupture; (4) the average systemic pressure obtained was too low.

In order to localize the pressure more to the left ventricle, a new type of balloon was constructed similar to the previous, except that it was included in a mantle of nylon cloth and was closed like a tobacco pouch around the cannula (Fig. 3A). The percentage relationship between the average femoral artery, pulmonary artery and pulmonary vein mean pressures to the controls was as follows:

	Mean pressures
Femoral artery	48 per cent
Pulmonary artery	125 per cent
Pulmonary vein	213 per cent

In these figures two improvements were observed: the femoral artery pressure had increased considerably and the pulmonary vein pressure was now only double that of the controls. The pulmonary artery pressure was 10 mm. Hg. higher than that of the pulmonary vein against controls which show a difference of 14 mm. Hg.

The results of the three experiments, pneumomassage and pumping with the two types of balloons as described were then compared with those pressure responses obtained by manual compression. The average mean of these pressures is represented as a percentage of the control means as follows:

	Mean pressures
Femoral artery	40 per cent
Pulmonary artery	160 per cent
Pulmonary vein	86 per cent

No important conclusion can be obtained from manual massage because the human factor enters predominantly into the problem. Fatigue comes within approximately three minutes when massaging rapidly at 100–120 compressions per minute. Massage at 70/minute could be maintained for 10 minutes with one hand. Whether the hand was in fatigue or not, the results are variable; slight displacement of the fingers from one area to another of the heart changes the pressure response in the pulmonary artery and systemic artery. Nonetheless, some interesting data have been collected, *i.e.*, (1) none of the participants produced any marked increase in pulmonary vein pressures which indicated that the operators were aware that the ventricles should be the chambers to be selectively compressed; (2) pulmonary artery means were high because compression was more effective over the thin walls of the right ventricle; (3) pressures began to drop off with fatigue; (4) better systemic pressures were obtained when the operators used their strongest hand. When the heart was compressed so that the thumb encircled the left ventricle and the fingers the right ventricle and when the participant massaged at a rate of 60-70 compressions per minute; pressures decreased as frequency increased above this rate.

The average pulmonary artery pressure means were 12 mm. Hg. above controls due to the excessive pressure of the fingers compressing the thin wall of the right ventricle. A low average femoral artery mean was obtained and varied continuously by as much as 60 mm. Hg. due to fatigue and inadequate technique.

If the heart is squeezed so that the thumb, which is the strongest finger, presses against the left ventricle, providing that it does not compress too near the conus, a better systemic pressure is obtained with little risk of the thumb rupturing the myocardium.[7-10]

Hand massage has the following advantages over mechanical heart compression: (1) no instruments other than a knife are essentially required. Respiration can be done mouth to mouth until the thorax is closed; (2) due to its "simplicity" it is the least time-consuming intervention. This factor is the most important of all as the survival rate drops considerably when massage is started after four minutes;[2-5] (3) a satisfactory pressure response in both the pulmonary and systemic circulation is better obtained if experienced hands are massaging.

Mechanical compression of the heart had the following advantages over manual massage: (1) pressures in the femoral artery were constant; (2) massage with an adequate balloon would be useful when the heart needed a prolonged period of compression for resuscitation; (3) it has proven to be much less traumatic to the heart with no risk of myocardial rupture.

Mechanical heart compression may prove to be of some use in surgery in those cases when the heart's condition is unstable after heart resuscitation. The balloon in this case could be placed behind the left ventricle under the pericardial sac with the pressure tube brought through a stab wound in the thoracic wall. In this way resuscitation would be possible without having to reopen the thorax. Likewise, during an abdominal intervention the balloon could be placed in the pericardial sac behind the left ventricle via a transdiaphragmatic approach with the tubing coming out through a wound in the midline of the epigastrium. We do not see any future in mechanical

heart compression outside of the surgery or emergency room. At the present time an attempt has been made to secure a more satisfactory balloon which is being made commercially for the purpose of future experimentation.

SUMMARY

General considerations concerning a realistic approach to heart resuscitation have been discussed.

Three methods of mechanical heart compression have been described, and the results obtained were compared with those of hand massage and controls.

Some opinions based on the experimental data obtained, as to the characteristics of the reciprocal advantages with manual heart massage, has been evaluated. ventricles of the heart, have been presented.

The possible application of mechanical heart compression, after due consideration of the reciprocal advantages with manual heart massage, has been evaluated.

ACKNOWLEDGEMENTS: We wish to express our appreciation to Mr. E. F. Andrews for his part in initiating this project and developing the instruments for its study. We also wish to thank Eleanor Humphreys, M.D. for her kind advice and study of the pathology of this project. We express our gratitude to Mr. W. Rank and Mr. H. Dotson for technical advice and assistance.

RESUMEN

Se diserta en general, sobre los métodos realistas para la resucitación cardiaca.

Se describen tres métodos de compresión cardiaca mecánica y los resultados obtenidos se han comparado con los del masaje manual y con los controles.

Se presentan las opiniones que se basan en los datos experimentales logrados con respecto a las características de un balón que puede considerarse ideal para la compresión selectiva de los ventrículos.

La aplicación posible de la compresión mecánica del corazón se valúa después de la consideración de las ventajas recíprocas con el masaje manual.

RESUMÉ

Les auteurs exposent les considérations générales au sujet d'une tentative vraiment pratique de résurrection cardiaque.

Trois méthodes de compression cardiaque mécanique ont été décrites et les résultats obtenus furent comparés à ceux des massages manuels et des témoins.

Les auteurs émettent quelques opinions sur les données expérimentales obtenues, comme sur les caractéristiques d'un ballon qui peut être considéré comme techniquement idéal pour une compression sélective des ventricules.

L'application possible de la compression cardiaque mécanique a été évaluée après estimation sérieuse des avantages comparés du massage cardiaque manuel.

ZUSAMMENFASSUNG

Diskussion allgemeiner Gesichtspunkte hinsichtlich eines wirklichkeitsnahen Weges zur Bekämpfung des Herzstillstandes.

Beschreibung von drei mechanischen Methoden der Herzkompression; die erzielten Ergebnisse wurden verglichen mit der manuellen Massage und Kontrolle. Darstellung gewisser Auffassungen, die sich auf die gewonnen eu Untersuchungsergebnisse stützen hinsichtlich der Eigenschaften eines Ballons, den man als technisch ideal für eine selektive Kompression der Herzkammern ansehen kann.

Auswertung der möglichen Anwendung der mechanischen Herzkompression nach gebührender Erwägung der reziproken Vorteile der manuellen Herzmassage.

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Unusual Complication of Pulmonary Arteriovenous Aneurysm: Intrapleural Rupture*

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Arteriovenous aneurysm of the lung may give rise to sequelae such as cyanosis, clubbed fingers and toes, polycythemia, dyspnea, hypertrophy of the heart and neurological changes resulting from paradoxical embolic processes.

A true complication of arteriovenous aneurysm is a rupture, which can result in hemoptysis or hemothorax. Hemoptysis due to intrabronchial rupture is a relatively frequent complication. According to Leutscher (1954) — in a monograph presenting a detailed analysis of 130 of the cases of arteriovenous aneurysm published up to 1954 — hemoptysis is mentioned as a complication in 25 per cent of cases. Hemoptysis occurred in three of the five cases hitherto reported from this clinic.

Intrapleural rupture of the arteriovenous aneurysm, resulting in hemothorax, however, proves to be an exceedingly rare complication which Leutscher found mentioned in only three of the 130 cases; it has not previously occurred in our material.

This paper describes a woman showing this unusual complication. The description is given both in view of the rarity and possible difficulties in diagnosing this condition, and in view of the fact that an emergency operation in recognized cases may be life saving.

CASE REPORT

A woman, aged 37, had Rendu-Osler disease and frequent epistaxis. In 1946 (at age 25) she began to cough, with occasional expectoration of blood-tinged sputum. In 1947, while walking in the open, she suffered a violent hemoptysis resulting in a collapse. X-ray film examination of the thorax at the time revealed a homogeneous, virtually round opacity with a diameter of about one inch beside the hilum of the left lung. There was a markedly positive Mantoux tuberculin reaction. There was no fever, nocturnal hyperhidrosis or emaciation. Repeated testing of sputum and fasting gastric contents for acid-fast rods remained negative. The process was nevertheless regarded as tuberculosis, and she was given treatment accordingly, by rest for 18 months. Subsequently she remained asymptomatic for several years. About 1950, she began to notice that dyspnea ensued more rapidly than previously. During the last five months preceding our examination, the left hemithorax was painful both in repose and during movements "as if inflamed." The pain radiated to the back, between the shoulder blades.

We saw a slightly cyanotic, somewhat dyspneic woman in good nutritional condition, with small telangiectases on the tip of the tongue, the upper and the lower lip and in the nail bed of several fingers. Fingers and toes showed no sign of clubbing. Physical examination of the thorax (Cardiological Department, Prof. Dr. D. Durrer) yielded the following findings. Lungs: vesicular respiration; resonant percussion sounds; lung-liver borderline: sixth rib in front and 12th thoracic posteriorly. There was moderate displacement of the pulmonary outline. Heart: one fingerbreadth enlargement to the left, with a diastolic souffle (grade 1) at the apex, A_2 of greater intensity than P_2. In the left anterior second intercostal space and on the back, medial to the apex of the right scapula, a vascular murmur was audible which occurred late during systole and did not resemble a typical diamond-shaped "stenotic" souffle. Pulmonary function was normal (vital capacity 116 per cent; one-second value 78 per cent). ECG: intermediary position of the heart; no anomaly. The oxygen saturation in the brachial artery was 92.5 per cent in repose, 88.5 per cent after two minutes' effort, and 97.5 per cent after 10 minutes' oxygen respiration. X-ray film examination revealed an opacity in the left upper and the right lower lobe; it appeared to be homogeneous, with smooth contours and showing pulsations at fluoroscopy. The condition was diagnosed as bilateral pulmonary arteriovenous aneurysm. This diagnosis was confirmed by angiocardiography. In the left upper and the right lower lobe,

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a sharply circumscribed contrast opacity was visible, with a thick, meandering branch of the pulmonary artery as afferent vessel and a wide branch of the pulmonary vein as efferent vessel (Figure 1).

She was advised to submit to surgical intervention in two stages. Since radiological findings showed that the arteriovenous aneurysm in the left upper lobe was probably the more superficially localized of the two aneurysms, the first operation was performed on the left lung.

A left-sided thoracotomy was done July 17, 1958 (Prof. Dr. I. Boerema). The arteriovenous aneurysm immediately became visible in the center of the upper lobe as a virtually round elevation of bluish colour and subpleural localization, slightly larger than the obtuse pole of a hen's egg. The aneurysm pulsated, and a thrill was palpable. The aneurysm was extirpated, the efferent and afferent vessels being ligated following deep dissection. The postoperative course was uneventful until the 13th postoperative day. On this day, the day after ambulation, she suddenly experienced violent pain in the posterobasal region of the right hemithorax, associated with marked dyspnea. There was no physical symptom of pleural irritation or exudation and no sign of peripheral thrombosis. Rupture of the arteriovenous aneurysm and pulmonary embolism were considered possible. It was expected that rupture of the aneurysm in this patient would cause marked hemoptysis, as had been the case in 1947. At this time, she produced only a small quantity of blood-tinged viscous sputum. The condidition was therefore diagnosed as pulmonary embolism, and treatment was instituted accordingly (with, among other measures, anticoagulant therapy using 10 mg. heparin per hour). The pain was considerably alleviated in the course of the two subsequent days. Percussion sounds were subdued over a handwidth zone in the posterobasal region, above which there was a markedly reduced respiratory murmur. Clinical and radiological data warranted no definite conclusion as to whether the case involved an infarction with fluid or atelectasis of an adhesive right lower lobe. Administration of heparin was discontinued on the 15th postoperative day in view of marked epistaxis. Violent attacks of pain in the right hemithorax recurred on the 18th postoperative day; she expectorated blood-tinged sputum. Bronchial respiration and reduced respiratory murmurs were audible in the posterobasal region; there was no pleural friction rub. In the absence of dyspnea, pulmonary embolism was improbable. There was a marked decrease in hemoglobin concentration. Intrapleural hemorrhage from the

FIGURE 1: Angiocardiogram. Arteriovenous aneurysm in left upper and right lower lobe.

arteriovenous aneurysm was then considered probable. Atelectasis of the right lower lobe was excluded by bronchoscopy. A thoracic puncture was performed, withdrawing 550 ml. blood. The previous muffling had decreased by a handwidth. After 18 hours, however, the subdued zone showed another upward enlargement, which a second puncture revealed to be attributable to 700 ml. blood. It was concluded from these two punctures that she had hemothorax which, after drainage, rapidly re-filled and which had to be attributable to a hemorrhage from the arteriovenous aneurysm. A right-sided thoracotomy (Prof. Dr. I. Boerema) had to be performed on the following day (August 8, 1958) in view of the serious loss of blood.

The pleural space contained an ample 1000 ml. of blood, and the pleural leaves in the region of the lower and middle lobe were covered by a layer of fibrin of 2 to 3 mm. thickness. Blunt removal of the fibrin layer offered no difficulty. On the antero-lateral side, there were adhesions between the lower lobe and the thoracic wall; after severence of the fibrinous adhesions, a pulsating dome the size of a marble became visible, above which a thrill was palpable. A small, firm clot on the top of the dome indicated the site of the rupture (Figure 2). Local excision of the aneurysm was performed. The postoperative course was uneventful, and she was discharged 14 days after the operation.

Comment

Wilkens (1917) described a woman aged 23, who suddenly died as a result of a left-sided hemothorax of 1500-200 ml. Autopsy revealed intrapleural rupture of an arteriovenous aneurysm.

Erf et al. (1949) described a 22-year-old man with an arteriovenous aneurysm in the left upper lobe, who collapsed following strenuous effort (pushing a car) and soon afterwards succumbed to a hemothorax of 1000 ml. Autopsy showed intrapleural rupture of the aneurysm.

Armentrout et al. (1950) reported of a woman aged 46 in whom a process, diagnosed at age 35 as a tumor, was recognized as an arteriovenous aneurysm. The history made mention of a spontaneous homolateral hemothorax 10 years before discovery of the so-called tumor. This hemothorax can be presumed to have resulted from intrapleural rupture of the aneurysm.

No other report on intrapleural rupture of arteriovenous aneurysms could be found in the literature after 1954. The first catastrophy in the right hemithorax in our patient remained unrecognized. The reasons

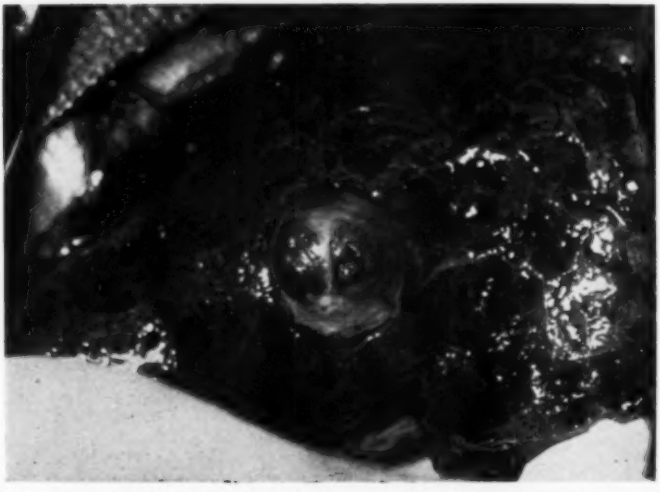

FIGURE 2: Superficially localized ruptured arteriovenous aneurysm in the right lower lobe. A small, firm clot at the apex indicates the site of the rupture.

are obvious, viz: 1) This complication is rare and, in sporadic reports, is mentioned as an incidental finding rather than as a true complication. 2) We were the first to have occasion to make exact observations on a woman with this complication from the very onset; our observations, therefore, could not be correlated with an established symptomatology. 3) The clinical picture of violent pain in hemithorax with marked dyspnea, occurring during the postoperative period on the first day after ambulation, is strongly suggestive of pulmonary embolism. Even after definite elimination of pulmonary embolism, the very rarity of intrapleural rupture of an arteriovenous aneurysm caused us to doubt the correctness of this supposition. The definite diagnosis, providing the indication for an emergency operation, was not made until after thoracic punctures had been performed. It may well be that the treatment instituted on the basis of the erroneous diagnosis of pulmonary embolism (i.e. anticoagulant therapy) caused aggravation of the hemorrhage during the first few days.

In retrospect, we have formed the following conclusions:

A. Intrapleural rupture resulting in hemothorax, like intrabronchial rupture resulting in hemoptysis, constitutes a true complication of pulmonary arteriovenous aneurysm.

B. It can be reasonably supposed that subpleural aneurysms are more likely to tend to intrapleural rupture than aneurysms localized deeper in the parenchyma.

C. The symptomatology of an intrapleural rupture may largely resemble that of pulmonary embolism.

D. If an acute intrathoracic catastrophy occurs in a patient with pulmonary arteriovenous aneurysm, particularly with one of subpleural localization, then a complicating intrapleural rupture of the aneurysm should be given serious consideration.

E. In the case of doubt, early thoracic puncture may be a valuable diagnostic aid.

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The Nature and Management of the Post-Commissurotomy Syndrome

The widespread use of surgical methods to correct cardiac diseases brought about a puzzling post-operative complication characterized by bouts of fever, thoracic pain and an inflammatory reaction of the pericardium, pleura and joints, with a polycylic and often recurrent course.

Although many cases are seen in the surgery of congenital heart malformation as well as other operations in which the pericardium is opened, the majority of the reported cases have appeared after the surgical correction of mitral stenosis.

Thus, the term most often employed is "post-commissurotomy syndrome" instead of the more correct designation of "post-pericardiotomy syndrome." The average frequency is around 25 per cent of the mitral operations. The signs and symptoms, in our personal observations, are the following:

(1) Fever of variable pattern, in all the cases;

(1) Fever of variable pattern, in all the cases.
the operative incision, radiating to the neck and shoulder. This is present in all the cases, and is sometimes very pronounced.

(3) Poly-arthralgia, most of the time without, but in some cases with, an inflammatory reaction. Present in 40 per cent of the cases.

(4) Pericardial rub, present in 50 per cent.

(5) Right pleural inflammatory reaction, not related to the thoracotomy, present in 20 per cent.

In all cases there was moderate leucocytosis, increased sedimentation rate and positive C-Reactive protein test.

Anti-streptolysin O titers are persistently below the normal upper limits.[2,3]

Electrophoretic studies in our laboratory[4] have shown in all the operated patients, even the asymptomatic ones, a significant increase in the α_2-globulin and a pronounced drop in the γ-globulin fraction. These changes are much more pronounced and last much longer in the commissurotomised patients than in those submitted to general surgery, even when these suffer from chronic rheumatic heart disease.

Penicillin and other antibiotics have no effect in the prevention or cure of the syndrome.

Corticoids give a dramatic relief of all the symptoms but do not affect the subsequent tendency to relapse.

Valvular sequelae have not been reported and the mechanical improvement obtained by the operation is not affected.

The pathogenesis of this curious complication is not well understood.

Most of the authors have discarded a rheumatic etiology for the syndrome because of the lack of evidence of streptoccocal infection, absence of valvular disease, and its appearance in non-rheumatic cardiac surgery.

The effect of the hemopericardium by itself, suggested by Papp and Zion[5] or Ito and Engle,[6] is difficult to accept in the production of a recurrent syndrome with late manifestations, sometimes many months after the operation.

Negative proof was also obtained by Haber, Sampson and Leeds[7] with the cases in which they purposely left a certain amount of blood in the pericardium.

The similarity with the "post-myocardial infarction syndrome," pointed out by Dressler,[8] lead the author, as well as Epstein,[9] to suggest the possible interference of an auto-immune mechanism.

Working along this line, we have prepared in our laboratory an auricular myocardium extract, using the auricular appendages excised at mitral surgery and tried a progressive pre-operative desensitization of the candidates for mitral commissurotomy.

The frequency of the post-commissurotomy syndrome dropped from 26 per cent to 7 per cent and the cases observed in the desensitized patients are much milder than in the untreated ones.

Furthermore, the serological pattern of all the patients changed and became more of the current post-operative type. A large proportion of these patients show a post-operative increase of the γ-globulin fraction instead of a drop.

This points to an auto-immune mechanism, but attempts to identify an antibody by the current methods (precipitation tests, imuno-electrophoresis) have given no positive results.

On the other hand, Kaplan,[10] from Cleveland, Ohio, using immunofluorescent anti γ-globulin demonstrated the existence in the sera of patients with post-commissurotomy syndrome of a globulin which may become firmly bound to certain myocardial structures.

One of my collaborators, H. Costa,[11] working in Kaplan's laboratory, points out that the places of fixation of the γ-globulin on a frozen section of myocardium are different in the syndrome from those where globulin from rheumatic patients are fixed.

Our personal opinion is that both rheumatic fever and post-commissurotomy syndrome, although of a different etiology, have a common denominator: the presence of an auto-immune mechanism.

For practical purposes we must accept the results of the desensitization and corticoid therapy as very useful tools.

We employed the approved method of Tufts for preparing non-denatured antigens in our myocardial extract. The extract is administered first in bi-weekly intradermal and, later sub-cutaneous injections, in doses of 0.10, 0.25, 1 and 2 cc., in the two weeks preceding operation.

In cases of failure of desensitization or in the unprepared cases developing the syndrome we used the cortisone derivatives, following the same plan, but using smaller dosage than in rheumatic fever.

Although the prognosis of the post-commissurotomy syndrome is uniformly favorable we can't ignore that its relapsing course may be very drawn out and as such disabling.

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CINE-ANGIOCARDIOGRAPHIC STUDIES OF THE OUTFLOW TRACT IN ISOLATED PULMONARY VALVULAR STENOSIS

Hemodynamic considerations have led to the concept of acquired infundibular muscular hypertrophy forming a further obstruction to the outflow of blood from the right ventricle in patients with severe isolated valvular pulmonary stenosis. An infundibular pressure gradient may become apparent following successful pulmonary valvotomy. This gradient can be reduced immediately by infundibular resection or may regress spontaneously over some months.

It is suggested that selective cine-angiocardiography of the right ventricular outflow tract and cardiac catheterization with combined recording of the pressure pulse and intracardiac electrogram provide the most complete analysis of the nature of the obstruction in pulmonary stenosis. The cine-angiocardiographic findings lend further support to the concept of infundibular obstruction from muscular hypertrophy and show narrowing of the infundibular lumen roughly proportional to the severity of the valvular pulmonary stenosis.

Watson, H., Pickard, C., Lowe, K. G., and Hill, I. G. W.: "Cine-angiocardiographic Studies of the Outflow Tract in Isolated Pulmonary Valvular Stenosis," *Brit. Heart J.*, XXII:708, 1960.

Marked Electrocardiogram Changes after Exercise

The six leads in the left column indicate leads I, II, III, V_4, V_5, and V_6, all taken at normal standardization. The patient gave a history of substernal discomfort, but the relationship of this discomfort to exercise, meals and emotion was not discrete. He was not obese; blood pressure was normal.

The resting electrocardiogram is probably within normal limits, although the amplitude of the T waves is somewhat greater than is usually seen in a 65 year-old man. The next four tracings were obtained immediately after, 2, 4 and 6 minutes of exercise. A marked depression of the RST segment occurred and with the passage of time, the T waves began inverting and the RST segment began returning to the base line. This change is most apparent in V_4, V_5 and V_6, although it is present in all six leads. The patient did not experience angina on this degree of exercise.

Changes of this degree and of this type in the electrocardiogram upon exercise in a man of this age practically are specific for ischemia of the myocardium. Changes due to potassium, digitalis, hyperventilation or medications are not of this particular identical nature and when this sequence of changes occurs on moderate exertion in a patient in the coronary age group, the physician would be justified in assuming an underlying ischemia of the myocardium, even if the patient is symptom-free.

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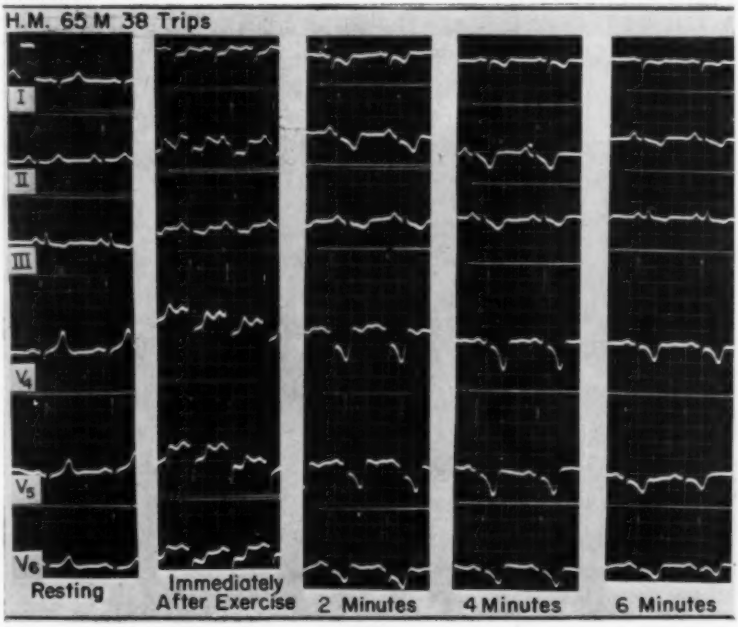

X-RAY FILM OF THE MONTH

Edited by Benjamin Felson, M.D.

Clinical History

This is a 68 year-old white man who was admitted with the chief complaints of pain in his right arm of nine months duration and a recent cold. He has had an occasional cough and has smoked 30 cigarettes daily for many years. There was no history of hemoptysis, shortness of breath, ankle edema or contact with tuberculosis.

Physical examination revealed an obese man in no acute distress with a right Horner's syndrome. No neck mass was present and examination of the chest was negative as was the remainder of the physical examination.

Laboratory work-up, including complete blood studies, bone marrow, aspiration, serology, sputa analyses, urinalyses, renal function studies, liver profile tests and EKG, was normal.

An eye consultation and sweat test were made to investigate the right Horner's syndrome which has been present for about five years without any additional eye symptoms. It was concluded that this was probably secondary to a mediastinal block of the cervical sympathetic chain.

Roentgen Examination: The chest was not remarkable. No pulmonary infiltration, consolidation, atelectasis or mediastinal adenopathy was found. Cervical spine films revealed hypertrophic osteoarthritic changes with degenerative narrowing of the intervertebral discs between C4-5, C5-6 and C6-7. Oblique views showed encroachment of intervertebral foramina by osteophytic spurs. These findings may have accounted for

From the Department of Radiology, US Veterans Administration Hospital, St. Louis, Missouri.

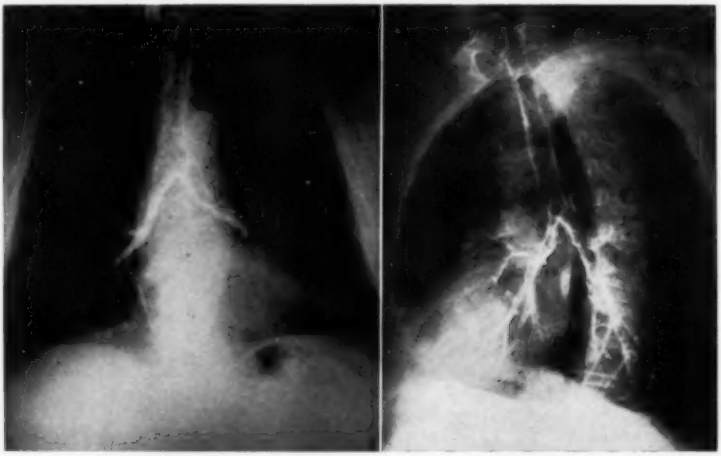

FIGURE 1A FIGURE 1B

the admission complaint of radicular pain which radiated down the right arm. Other roentgen studies including intravenous pyelography, upper GI series, barium enema and a metastatic bone survey were negative. It was decided to investigate the mediastinum further by means of bronchoscopy, bronchography and esophagoscopy in search of an explanation for his right Horner's syndrome and possibly for his radicular right arm pain.

ANSWER: ***Primary Amyloidosis of the Trachea and Bronchi.***

Bronchography outlined numerous filling defects, scalloping and smooth indentations along the tracheobronchial airway. Both the trachea and major bronchi were grossly involved. No atelectasis, consolidation or bronchiectasis was present in either lung. However, moderate generalized pulmonary emphysema was present.

On bronchoscopy, numerous nodular lesions were found throughout the trachea and major bronchi. The overlying mucosa everywhere, however, was intact. Multiple pink and tan specimens were taken with a basket biopsy forceps. Microscopically the fragments were lined with epithelial tissue on one side with the major portion of the specimen made up of an eosinophilic hyaline material which took a congo red stain. The histological diagnosis was amyloidosis.

Esophagoscopy was negative. No other evidence of amyloid disease, either primary or secondary, was found elsewhere in the body. On discharge the diagnoses were:

1. Amyloidosis, primary, involving the trachea and bronchi.
2. Cervical ostearthritis, hypertrophic.

His subsequent course over the next four years until the present time has been uneventful. His Horner's syndrome and right arm pain remain unchanged and he is without additional symptoms. Recent bronchoscopic examinations reveal less amyloid tissue in his tracheobronchial airway than was initially seen. Laboratory studies including congo red tests remain essentially negative. He has had no respiratory symptoms and maintains a full active life in apparently good health.

Discussion

Amyloidosis of the respiratory tract is a rare condition. Approximately two dozen authenticated cases have been reported in the literature,[5] most of these having been diagnosed at autopsy.

The signs and symptoms are an expression of the physical size and location of the amyloid tumors. In other cases these have included hoarseness, dyspnea, cough, wheezing, hemoptysis, recurrent pneumonia and bronchiectasis.[6] In this case the admission complaint was unrelated to the disease process, namely pain radiating to the right arm resulting from cervical osteophytosis. The findings on physical examination of a right Horner's syndrome led to further investigation of the mediastinum by means of endoscopy and bronchography.

A clinicopathologic classification[3] includes: 1) primary amyloidosis, 2) secondary amyloidosis, 3) tumor-forming amyloidosis and 4) amyloid associated with tumors such as multiple myeloma, etc. The distinguishing characteristics between these divisions of amyloidosis often overlap, strongly implying some unitary concept of its pathogenesis.[6]

Cases have been reported in which localized amyloid deposits have gone on to become a diffuse and generalized disease. In the present case the amyloid was present in the trachea and bronchi but demonstrated in no other site. The presence however of a right Horner's syndrome would also imply mediastinal involvement of the cervical sympathetic chain also.

The form of treatment naturally depends upon the physical location of the amyloid tumors. Within the trachea and main bronchi, simple bronchoscopy with local excision of the tumefaction is an efficient method. The prognosis is good.

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The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with a brief history. Please submit material to: Benjamin Felson, M.D., Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

INTERMITTENT COLD CORONARY PERFUSION AS AN ADJUNCT TO OPEN HEART SURGERY

Elective arrest of cardiac muscular activity during cardiopulmonary bypass can be produced by selective cooling of the myocardium. This is accomplished by perfusion of the coronary arteries with cold, oxygenated blood at predetermined flow rates of 30 to 150 cc. per minute. A rapid reduction in myocardial temperature occurs, resulting in hypothermic arrest of the heart at a mean temperature of 14°C. Interruption of coronary perfusion is then possible for multiple periods of 15 to 25 minutes, providing a dry, quiet operative field.

Spontaneous rewarming of the myocardium takes place during the absence of perfusion due to contact between the heart and the normothermic mediastinal structures. For this reason, intermittent coronary perfusion is obligatory. The observed metabolic requirements of the heart are rapidly satisfied by the flow of oxygenated blood, and this permits subsequent interruption of coronary circulation.

Bernhard, W. F., Schwarz, H. F., and Mallick, N. P.: "Intermittent Cold Coronary Perfusion as an Adjunct to Open Heart Surgery," *Surg., Gynec., and Obstet.*, 111:6, 1960.

EFFECTS OF CARBON DIOXIDE ON THE CARDIOVASCULAR SYSTEM

Various cardiac arrhythmias, of which the most important are ventricular, can occur both during hypercarbia and during its correction. Increased activity of the sympathetic nervous system certainly is, and ionic flux through the myocardial surface may be, involved in these responses.

Price, H. L.: "Effects of Carbon Dioxide on the Cardiovascular System," *Anesthesiology*, 21:652, 1960.

CHAPTER NEWS

ARIZONA CHAPTER

The annual meeting of the Arizona Chapter of the College will be held at the Safari Hotel in Scottsdale, April 27, at which time the following program will be presented:

"Bronchoscopy and Bronchography in Diagnosis of Pulmonary Diseases"
H. Corwin Hinshaw, San Francisco, California

"Retrograde Thoracic Aortography"
Herbert L. Abrams, San Francisco, California

ILLINOIS CHAPTER

The Illinois Chapter recently donated the sum of $50 to the Council on Research of the College in memory of the late Dr. George H. Vernon.

LOUISIANA CHAPTER

The Louisiana Chapter will sponsor a series of case presentations at its annual meeting at the Veterans Administration Hospital, New Orleans, March 10. Cases will be presented by the following physicians: Page Acree, Baton Rouge; Oscar Alvarez, Lafayette; William Fey, Lake Charles; Walter McCook, Shreveport; and Zotlan Mann, Alexandria. The following New Orleans physicians will serve as a panel of consultants for the case presentations: Oscar Blitz, Howard A. Buechner, Charles Dunlap, Leo Horan, Sydney Jacobs, Charles Nice, Robert Schramel, John H. Seabury, Lawrence H. Strug, Morton Ziskind, and Herman J. Moersch, Chicago, Illinois.

OHIO CHAPTER

The Ohio Chapter will meet in conjunction with the meeting of the Section on Internal Medicine of the Ohio State Medical Association on April 12 in Cincinnati. The chapter program is as follows:

"Recent Advances in the Diagnosis and Treatment of Fungus Diseases of the Lungs"
Arthur M. Olsen, Rochester, Minnesota

"Treatment of Combined Pulmonary and Cardiac Insufficiency"
Joseph M. Ryan, Columbus, Ohio

NEW JERSEY CHAPTER POSTGRADUATE COURSE

A postgraduate course on cardiopulmonary diseases, sponsored by the New Jersey Chapter of the American College of Chest Physicians, is scheduled for the first four Wednesdays during March. The dates for the course, which will be held at the Essex House Hotel in Newark, are March 1, 8, 15 and 22, from 1 to 5 p.m. For information, please write: Dr. A. A. Peckman, 2511 Hudson Boulevard, Jersey City, New Jersey.

NEW YORK STATE CHAPTER

The 21st annual clinical meeting of the New York State Chapter of the College will be presented at New York University School of Medicine, New York City, on March 24, in cooperation with the university. The following program will be presented in the Alumni Hall Auditorium:

Morning Session
Charles E. Hamilton, Brooklyn, Chairman

9:10 a.m. Welcoming remarks
George B. Armstrong, New York City

9:15 a.m. Symposium on Pulmonary Emphysema
"Pathogenesis and Pathology"
William E. Loring, New York City
"Physiology"
Rejane M. Harvey, New York City
"Treatment"
John H. McClement, New York City

11:00 a.m. Question and answer period

11:15 a.m. Chest X-ray Conference
Maxwell H. Poppel and David Ulmar, New York City, Moderators

12:30 p.m. Luncheon
"New Directions in Chemotherapy"
Daniel G. Miller, New York City

Afternoon Session
Samuel A. Thompson, New York City, Chairman

2:00 p.m. "Diagnostic Criteria and Procedures in Cardiac Disease"
Edmund H. Reppert, New York City
"Surgical Aspects in Cardiac Disease"
George R. Holswade, New York City

3:30 p.m. Clinico-pathological Conference
Willard J. Davies, Rockville Center; Lawrence P. Shea, New York City, Moderators

IMPORTANT

27th Annual Meeting, American College of Chest Physicians
Hotel Commodore, New York City, June 22-26, 1961

Joint Meeting with American Medical Association, Monday, June 26

The 27th Annual Meeting of the American College of Chest Physicians in New York City in 1961 will be another milestone in the history of the College. This year, a joint session of the Section on Diseases of the Chest of the American Medical Association and the American College of Chest Physicians will be held on Monday, June 26, the first such meeting in the history of the two societies. The joint session will follow the scientific assembly of the College which opens on Saturday, June 24, instead of on Friday, as in the past. Developed by the Committee on Scientific Program of the American College of Chest Physicians and the Section on Diseases of the Chest of the American Medical Association, this joint program, planned as an action of the Board of Trustees of the AMA and the Board of Regents of the College, will be highlighted by a number of features of special interest.

On Monday, June 26, the combined meeting of the Section on Diseases of the Chest of the American Medical Association and the American College of Chest Physicians will open at the Coliseum. This will include a symposium on "New Approaches in the Treatment of Acquired Heart Disease," a panel on "Steroid Treatment in Lung Disease," and a symposium on "Modern Diagnostic Measures in Cardiac Disease."

The always popular Fireside Conferences will again be an important part of the program. This year, these too are sponsored jointly with the American Medical Association. Accordingly, these Fireside Conferences, usually held on Friday, will be held this year on Monday, June 26, as part of the joint session. They will consist of 36 round tables with prominent scientists discussing the most recent advances in cardiopulmonary diseases.

The round table luncheons, for many years an attractive feature of the College program, will extend through Monday, June 26, as a part of the joint session. This year, there will be 21 luncheons beginning with three on Friday, June 23, and six each on Saturday, Sunday and Monday, with the customary excellent panelists.

College Scientific Program

One of the new features of the College scientific sessions this year will be two cine-symposiums, one on "Fibrinolytic Therapy in Acute Coronary Thrombosis" and the other on "Thoracic Surgical Emergencies in Infants." Each will consist of a moderator and four panelists, the first three presenting a film and commentary and the fourth evaluating the discussions. This will be followed by a question and answer period.

The regular scientific program of the College meeting will include outstanding papers by eminent scientists discussing recent advances in the diagnosis and treatment of pulmonary and cardiovascular diseases. As usual, both medical and surgical aspects will be well covered, including symposiums and panel discussions on: "What's New in Cardiovascular Surgery, The New and the Old in Treatment of Hypertension, Circulation in Newborn Infants, Emphysema, and Medical Aspects of Air Pollution.

A series of special presentations consisting of research papers on the latest developments in the cardiovascular and bronchopulmonary fields has been scheduled for Sunday afternoon.

Other Features

As part of the excellent scientific exhibits of the American Medical Association meeting, a College exhibit on "Physiologic and Clinical Testing of Cardiac Function" has been approved by the Council on Scientific Assembly of the AMA. Produced by the College Committee on Cardiovascular Physiology, this exhibit parallels our annual exhibit on "Pulmonary Function Testing" arranged by the Section on Diseases of the Chest and the College. The scientific exhibits will open at the Coliseum on Sunday afternoon.

The customary postgraduate seminars, one-day refresher courses in chest medicine, will be held on Thursday, June 22. Two special seminars have been prepared—an Open Forum on "The Chest Conference Approach to Undergraduate Teaching," and another on "Unsolved Problems in the Prevention and Treatment of Tuberculosis."

There will be a meeting of the New York State Chapter of the College on Friday, June 23 and all members of the College are invited to attend. Dr. Herman E. Hilleboe will deliver the Howard Lilienthal Lecture, "Tuberculosis in the Changing World."

The combined session with the American Medical Association will enable members of the College to attend the annual meetings of both organizations over a minimum period of time. The interest already indicated gives promise of a record attendance. It is not too early to make hotel reservations. We urge you to make your plans now and to send your reservations in at once.

27th ANNUAL MEETING
New York City

Outline of Events

Thursday, June 22

Postgraduate seminars
Examinations for Fellowship
Meeting, Executive Council

Friday, June 23

Annual meeting, Board of Regents
Open Forums
- Council on Undergraduate Medical Education
- Committee on Tuberculosis

Joint meeting, Board of Governors and Board of Regents
Open administrative meeting
Council and committee meetings
Round table luncheon meetings
New York State Chapter meeting
- Howard Lilienthal Lecture

Saturday, June 24

Scientific sessions
- Cine-symposiums
  - Fibrinolytic therapy in acute coronary thrombosis
  - Thoracic surgical emergencies in infants

Round table luncheon meetings
Motion picture session
Symposium on medical aspects of air pollution
Emphysema and pulmonary physiology
Cardiovascular problems in children, including the newborn

Sunday, June 25

Scientific sessions
- Tuberculosis and other pulmonary diseases
- Tumors and pulmonary physiology
- Coronary diseases and myocardial disease
- Visual aids in cardiologic diagnosis and treatment
- Panel discussions
  - The new and old in the treatment of hypertension
  - What's new in cardiovascular surgery

Motion picture sessions
Round table luncheon meetings
Convocation
- Louis Mark Memorial Lecture

Cocktail party
President's banquet
Dance

Monday, June 26

JOINT MEETING WITH AMERICAN MEDICAL ASSOCIATION
Scientific Session
(New York Coliseum)

Symposium on new approaches in treatment of acquired heart disease

Panel discussion on steroid treatment in lung disease

Symposium on modern diagnostic measures in cardiac disease

Scientific papers on pulmonary disease

Round table luncheon meetings
(Park Sheraton Hotel)

Fireside Conferences
(Hotel Commodore)

36 tables, prominent scientists discussing recent advances in cardiopulmonary diseases

Tuesday, June 27

JOINT MEETING, SECTION ON DISEASES OF THE CHEST AND SECTION ON GENERAL PRACTICE OF AMERICAN MEDICAL ASSOCIATION
(New York Coliseum)

Panel discussion on treatment of angina of effort
Symposium on present status of newer entities in pulmonary diseases

Wednesday, June 28

JOINT MEETING, SECTION ON DISEASES OF THE CHEST AND SECTION ON RADIOLOGY OF AMERICAN MEDICAL ASSOCIATION
(New York Coliseum)

Symposium on roentgenology of cardiovascular diseases

Panel discussion on fundamentals of chest roentgenology

All sessions, Thursday through Sunday, June 22-25, will be held at the Hotel Commodore

Convocation and Banquet

The outstanding College social function of the year, The Presidents' Banquet, will be held on Sunday, June 25, with cocktails and a dance sponsored by the New York State Chapter. The annual Convocation will also be held on Sunday and the Honorable Warren E. Burger, U. S. Circuit Court judge, will present the Louis Mark Memorial lecture, "Medicine and the Law." A special program of interest to the ladies has been prepared under the chairmanship of Mrs. Henry Heimlich, Rye, New York.

REPORT OF THE COMMITTEE ON BYLAWS

The following amendment to the bylaws was approved by the Board of Regents at its Semi-annual Meeting in Washington, D. C., November 28, 1960:

ARTICLE XI, Section 1: (g)

The following sentence is to be inserted after the word "Committee" (line 15, page xviii):

> The Governor of the College in each state where a chapter of the College exists, as well as the Regent of the College in the district, shall serve as ex-officio members of the Executive Committee of their respective state chapters and shall receive notification in writing of all meetings of the Executive Committee of their respective state chapter.

The amendment will be voted upon by the membership of the College at the Open Administrative Session on Friday, June 23, during the 27th Annual Meeting in New York City.

CARL H. GELLENTHIEN
Chairman

NEW JAPANESE HEART JOURNAL

The first two issues of the *Japanese Heart Journal* arrived recently. This is a quarterly publication issued by the Second Department of Internal Medicine of the Faculty of Medicine at the University of Tokyo in Japan. The editor-in-chief is Dr. Hideo Ueda, F.C.C.P., Professor of Internal Medicine at the University of Tokyo. Dr. Ueda has an excellent advisory board and an outstanding editorial board. The technical editors are well-known.

This journal is a splendid contribution to the field of cardiology. We have recognized for years the fine clinical studies made by the Japanese physicians and have also been aware of the outstanding clinical and basic research done by our colleagues in Japan. It was disappointing to many of us that much of this material was not available because of language barriers. This new journal now makes it possible for all of the cardiologists in the world to become familiar with the Japanese contributions to the science of cardiovascular disease.

The format of the journal is exceptionally well done. The paper is of fine quality, and the contents of the journal reveals an excellent selection of material by the editorial board. All in all, this new heart journal is now a must for all cardiologists.

JOHN F. BRIGGS, M.D.
St. Paul, Minnesota

ELECTION OF OFFICERS

Election of officers of the College for the 1961-62 term will be held on Friday, June 23, at the Open Administrative Session of the 27th Annual Meeting of the College in New York City, June 22-26. Recommendations for elective offices may be addressed to: Dr. Donald R. McKay, Chairman of the Committee on Nominations, 1275 Delaware Avenue, Buffalo, New York. Other members of the committee are Drs. Alexander Libow, Miami Beach and Henry C. Sweany, Mt. Vernon, Missouri.

MEDICAL SERVICE BUREAU

POSITION WANTED

Surgeon—Thoracic surgeon, 35, American, AOA, progressive university residency, Board diplomate, F.C.C.P., F.A.C.S., dissatisfied with three years' solo private practice. Desires clinical surgical association with group, clinic or medical school with teaching and some clinical research. Prefers southeast. Please address inquiries to Box 312B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Pulmonary Disease Service—two staff physician positions available on a 225-bed chest service with active medical, surgical and pulmonary functions. Salary from $10,635 to $17,000 p.a., depending on qualifications and experience. Living quarters available on station at moderate cost. Liberal retirement, vacation and sick benefits. Requirements: American citizenship, graduate class A medical school, and a state board license. Address inquiries to the Manager, VA Center, Martinsburg, West Virginia.

Physician wanted to work in division of pulmonary diseases. Must be licensed by a state or have immigrant visa and be certified by ECFMG. Active medical and surgical program for all types of diseases of the chest. Large out-patient clinic. Training in cardiopulmonary laboratory provided, including catheterization. Good salary. Available immediately. Apply to: Dr. Rufus Little, Superintendent, Bergen Pines County Hospital, Paramus, New Jersey.